



# SURGERY

A Monthly Journal Devoted to the Art  
and Science of Surgery

## Editors

ALTON OCHSNER  
New Orleans

OWEN H. WANGENSTEEN  
Minneapolis

## Associate Editor

ALFRED BLALOCK  
Baltimore

## Advisory Council

DONALD C. BALFOUR, Rochester, Minn.

VILRAY P. BLAIR, St. Louis

BARNEY BROOKS, Nashville

ELLIOTT C. CUTLER, Boston

WILLIAM E. GALLIE, Toronto

EVARTS A. GRAHAM, St. Louis

HOWARD C. NAFFZIGER, San Francisco

HARVEY B. STONE, Baltimore

ALLEN O. WHIPPLE, New York City

## Editorial Board

FREDERICK A. COLLIER, Ann Arbor

EDWARD D. CHURCHILL, Boston

VERNON C. DAVID, Chicago

LESTER R. DRAGSTEDT, Chicago

RALPH K. GHORMLEY, Rochester, Minn.

ROSCOE R. GRAHAM, Toronto

SAMUEL C. HARVEY, New Haven

FRANK HINMAN, San Francisco

EMILE F. HOLMAN, San Francisco

EDWIN P. LEHMAN, University, Va.

FRANK L. MELENEY, New York City

JOHN J. MORTON, Rochester, N. Y.

THOMAS G. ORR, Kansas City, Kan.

WILDER G. PENFIELD, Montreal

ISIDOR S. RAYDIN, Philadelphia

MONT R. REID, Cincinnati

WILLIAM F. RIENHOFF, JR., Baltimore

---

VOLUME 11

JANUARY—JUNE, 1942

---

ST. LOUIS  
THE C. V. MOSBY COMPANY

1942



COPYRIGHT, 1942, BY THE C. V. MOSBY COMPANY

*(All rights reserved)*

Printed in the  
United States of America

*Press of  
The C. V. Mosby Company  
St. Louis*

# SURGERY

VOL. 11

JANUARY, 1942

No. 1

## Original Communications

### THE EFFECT OF BILE SALTS ON RECOVERY OF LIVER FUNCTION AFTER RELEASE OF COMMON DUCT OBSTRUCTION\*

A. L. BERMAN, PH.D., E. SNAPP, M.S., AND A. C. IVY, M.D.,  
CHICAGO, ILL.

*(From the Department of Physiology and Pharmacology, Northwestern University  
Medical School)*

THERE IS the impression in surgical and clinical medicine that the administration of bile salts, orally or intravenously, will increase the rate of elimination of bile pigments accumulated in the blood stream because of biliary obstruction or liver damage. A number of surgeons, such as Boyce<sup>1, 2</sup> and Finsterer<sup>3</sup> have used dehydrocholic acid intravenously in the postoperative management of patients in whom gall bladder or biliary tract surgery had been performed. They report an improvement in the general condition of the patients and a decrease in the intensity of the jaundice, as well as an increased "flushing out" effect of the biliary passages. However, they present no accurate studies on the rate of elimination of bile pigment, and one simply gets the impression that a decrease in jaundice occurred simultaneously with the use of bile salts. Appel and Jankelson<sup>4, 5</sup> used sodium dehydrocholate in arsenical hepatitis due to neoarsphenamine injections, and although their data and results are not decisive they conclude that recovery from jaundice and toxic hepatitis due to arsenical drugs was greatly facilitated in many cases by the use of sodium dehydrocholate. It is obviously difficult, if not impossible, to control such observations, in view of the fact that the hepatic damage present is subject to wide variation. This is evidenced by the fact that (a) in severe hepatitis bile salts do not provoke a choleresis and are not eliminated in the bile; (b) after the release of obstruction bile salts may not appear in the bile for from two to ten or more days; and (c) in the presence of a normal liver a choleresis produced by bile salts does not increase the

\*This work was aided by the R. L. Dawkins and Marjorie Newman Research Grants.  
Received for publication, March 26, 1941

elimination of bile pigment. Such evidence does not preclude the possibility, however, that when the liver does recover sufficiently to be stimulated by bile salts, their administration will not increase the elimination of pigment when much is present in the body. Yet, it must be remembered that much of the pigment in jaundice is in the tissue where it is relatively fixed, as compared to that in the circulation. A search of the literature has not revealed adequately controlled experiments which demonstrate that the use of bile salts increases the rate of removal of bile pigment from the blood.

An investigation of this question was begun. In our first experiments<sup>6</sup> anesthetized biliary fistula dogs were used and jaundice was produced by the intravenous injection of large amounts of commercially prepared bilirubin. From this study we concluded that the constant injection of 0.6 or 6.0 Gm. of sodium dehydrocholate per hour did not increase the rate of removal of intravenously injected bilirubin. However, specific mention was made, at that time, that these results would not necessarily hold true for unanesthetized dogs or human beings after the relief of common duct obstruction. Since it is difficult to obtain patients with the same degree and duration of jaundice, it was felt that this problem could best be solved by using accurately controlled unanesthetized animals. This report is concerned with the results obtained on animals "jaundiced" for the same length of time, some of which were given large doses of bile salts after the relief of common duct obstruction, while others were used as controls.

#### METHODS

Healthy dogs weighing between 8 and 14 kg. were used. Before operation, the animals were observed on our diet for approximately one week, and those that manifested anorexia or distemper were discarded. A total of twenty dogs was divided into two equal groups of ten dogs each; one group received bile salts, while the other group served as a control. At the first operation, under ether anesthesia, the common duct was doubly ligated and approximately 5 mm. of the duct resected between the ligatures; the gall bladder was removed. All the dogs recovered rapidly and were allowed to remain obstructed for a period of seven days. During this time they were fed the standard diet of commercial dog food and milk and were observed daily for signs of increasing jaundice, infection, anorexia, and general condition. At the end of this seven-day period, the bilirubin content of the blood and urine was determined according to the method of Gibson and Goodrich.<sup>7</sup> These data represent the "preoperative" bile pigment values due to occlusion of the biliary passages (Tables I, II, and III). After this period of obstructive jaundice, the animals were reoperated upon under ether anesthesia and the obstruction removed by making a biliary fistula of the Rous-McMaster type.<sup>8</sup> This was done by putting a catheter into the proximal portion of the cut common duct

TABLE I  
RATE OF ELIMINATION OF BILE PIGMENT FROM BLOOD AND URINE AFTER RELEASE OF 7-DAY COMPLETE BILIARY OBSTRUCTION  
(CONTROL GROUP)

NO. AND WEIGHT OF DOG		DAYS OF OBSTRUCTION	BLOOD BILIRUBIN		URINE BILIRUBIN		TOTAL CHOLIC ACID		DIET
NO.	Kg.		PREOPERATIVELY MG./100 C.C.	NORMAL IN DAYS	PREOPERATIVELY MG./100 C.C.	NORMAL IN DAYS	MG./24 HR.	NORMAL IN DAYS	
1	9.5	7	24.8	4	13.6	3	1,246	5	3
2	10.0	7	3.3	4	—	4	1,014	6	3
3	13.0	7	6.3	5	18.0	4	1,010	3	3
4	8.4	7	2.8	4	8.1	4	1,486	4	2
5	11.1	7	7.3	13	9.4	12	1,054	10	8
6	8.4	7	4.1	4	9.0	2	1,412	4	2
7	8.1	7	10.6	12	11.6	12	840	9	9
8	12.0	7	10.0	4	8.7	4	1,187	3	2
9	12.0	7	10.2	6	23.9	4	1,495	5	2
10	9.0	7	9.7	6	23.5	5	1,093	4	4
Average	10.1	7	8.9	6.2	13.9	5.4	1,187	5.3	3.4

TABLE II

EFFECT OF KETOCHOLANIC ACIDS IN PROMOTING ELIMINATION OF BILE PIGMENT FROM BLOOD AND URINE AFTER RELEASE OF 7-DAY COMPLETE BILIARY OBSTRUCTION (BILE-SALT GROUP)

NO. AND WEIGHT OF DOG		DAYS OF OBSTRUCTION	BLOOD BILIRUBIN		URINE BILIRUBIN		TOTAL CHOLIC ACID		DIET
No.	Kg.		PREOPERATIVELY MG./100 C.C.	NORMAL IN DAYS	PREOPERATIVELY MG./100 C.C.	NORMAL IN DAYS	MG./24 HR.	NORMAL IN DAYS	
1	10.0	7	6.8	6	3.6	6	1,464	4	3
2	12.0	7	8.5	4	7.5	3	1,020	6	3
3	11.1	7	6.2	5	8.0	5	1,800	3	2
4	10.0	7	3.0	4	6.5	3	1,053	6	5
5	10.0	7	8.3	5	21.0	5	1,016	7	5
6	8.4	7	4.5	5	2.2	3	896	6	Ate very little
7	9.0	7	4.5	5	2.9	3	782	6	Ate very little
8	10.5	7	9.0	6	13.2	6	972	6	2
9	8.1	7	5.6	5	15.4	3	1,050	6	3
10	10.0	7	8.8	7	4.5	6	1,306	4	2
Average	9.9	7	6.72	5.3	8.48	4.3	1,136	5.4	3.0

TABLE III  
COMPARISON OF AVERAGE RESULTS OBTAINED IN CONTROL AND BILE-SALT GROUPS

NO. AND WEIGHT OF DOG		DAYS OF OBSTRUCTION	REGIME	BLOOD BILIRUBIN		URINE BILIRUBIN		TOTAL CHOLIC ACID		DIET
No.	Kg.			PROPERA- TIVELY MG./100 C.C.	NORMAL IN DAYS	PROPERA- TIVELY MG./100 C.C.	NORMAL IN DAYS	MG./24 HR.	NORMAL IN DAYS	
10	10.4	7	Control average range	8.9 2.8-21.8	6.0 4-13	13.9 8.1-24	5.0 3-12	1,187	5.0 3-10	3
10	9.9	7	3 Gm. ke- tochol/ day range	6.7 4.5-9.0	5.0 4-7	8.5 2.2-21	4.0 3-6	1,136	5.0 3-7	3

and bringing the rubber tubing to the outside, where the bile was collected in a rubber balloon which was attached to the outside of the dog's binder. One group of ten animals was fed 3 Gm. of keto-cholanic acid (ketochoh) daily with the meals; the other group was not given any bile salts. We have used this bile salt preparation since we knew from previous studies<sup>9</sup> that this preparation is a potent cholérétique and would possibly have as much effect on the elimination of bile pigment from the blood as any of the bile salt preparations. The animals were then observed until the jaundice disappeared and the pigment content of the blood and urine became negligible. Daily blood and urine van den Bergh determinations were made to follow the pigment excretion, and the bile was analyzed for cholic acid according to the Reinhold and Wilson modification of the Gregory-Paseoc method.<sup>10</sup> Those animals that did not eat or those that showed signs of infection and obstruction were not included in the results. If they were included, our experiment would not be adequately controlled; i.e., we have kept conditions as uniform as possible, except for the presence or absence of bile salts and choleresis.

#### RESULTS

*Pigment Excretion.*—**CONTROL GROUP.**—After seven days of biliary obstruction, the blood bilirubin concentration averaged 8.9 mg. per cent (range 3.0 to 24.8 mg. per cent), while the urine bilirubin concentration averaged 13.9 mg. per cent (range 8.0 to 23.9). The average time for the disappearance of the bile pigment from the blood and urine was six and five days, respectively. Most of the animals had normal urine and blood pigment concentrations in three or four days, but in two cases, Dogs 5 and 7, approximately two weeks were required for the complete removal of the excess pigment. These two dogs did not eat so well as the others, which means they were more affected by the condition than was indicated by the bilirubin data or the intensity of jaundice.

**BILE-SALT GROUP.**—When 3 Gm. of keto-cholanic acid was administered daily the accumulated bile pigment was removed from the blood in five days and disappeared from the urine in four days. The preoperative blood and urine pigment concentrations were 6.7 and 8.5 mg. per cent, respectively, which was slightly less than the values obtained in the control group. Tables I and II give the results of the individual groups and Table III contains the average results as a basis for comparison. It is obvious from these results that the administration of a potent cholérétique in large daily doses did not significantly increase the rate of removal of bile pigment from the blood.

*Recovery of Cholic Acid Output.*—What effect does the administration of bile salts have on the speed of recovery of cholic acid synthesis after the relief of common duct obstruction? In this work we had an

excellent opportunity to study and attempt to answer this practical clinical question. In both groups, cholic acid was found in the bile specimens during the first day after release of the common duct obstruction. The concentration of cholic acid became normal in one or two days, but the total daily cholic acid output did not become normal, in both the control and bile-salt group, until the fifth postoperative day on the average. None of the animals approximated normal total cholic acid output in less than three days, while only three of the twenty dogs took more than six days for cholic acid recovery. The average total daily cholic acid output in the control group was 1,187 mg., the range being from 840 to 1,495 mg. per day. In the bile-salt group the average daily output was 1,136 mg. with a range of 782 to 1,464 mg. These average figures compare favorably with the normal control values obtained in a previous study<sup>9</sup> on approximately seventy-five biliary fistula dogs. Thus, it is quite apparent that the administration of bile salts did not increase the speed of cholic acid recovery after relief from biliary obstruction. The results of previous studies show that cholic acid synthesis is not affected by ketochol or the ketocholanates, which is the reason why ketochol is advantageous for a study of this type. If we had used natural bile salts or nonoxidized cholic acid derivatives, we should have had to calculate cholic acid synthesis.<sup>9</sup>

#### DISCUSSION

By a series of controlled experiments we have attempted to answer the question: "Does the administration of bile salts increase the speed of disappearance of jaundice and return of cholic acid output after the relief of biliary obstruction?" It is evident from the results shown in Table III that large doses of ketocholanate acid had no significant effect on the rate of elimination of bile pigments from the blood and urine, though the average trend, which may have been due to chance, is favorable. The bile pigment was removed from the blood and urine in the control group in six and five days, respectively; five and four days, respectively, in the bile-salt series. Although there is a difference of one day between the control and bile-salt groups, this is in no way statistically significant, especially since there was much overlapping in the two groups, and since the preoperative blood and urine pigment concentrations in the treated group was less than the control group. We find that these results may have been predicted by the results obtained on total pigment output when large doses of bile salts and acids were administered to normal dogs and normal biliary fistula dogs. Dragstedt and Mills<sup>11, 12</sup> in a few experiments on unanesthetized dogs found that the intravenous injection of sodium dehydrocholate had no effect or appeared to augment slightly the rate of removal of intravenously injected bilirubin. In previous studies<sup>9</sup> we found that the daily administration of 3 and 5 Gm. of the salts of various bile acid preparations



to healthy biliary fistula dogs *did* not increase the daily pigment output over the control values. Thus, we have shown that the administration of bile salts will not definitely increase the rate of removal of bile pigment from the blood in normal and pathologic experimental animals.

Since the bile acids have been shown to be a product of the liver exclusively,<sup>13</sup> a number of investigators have determined the bile acid concentration in drainage bile and have used this test as an index of hepatic function. Greene, Walters, and Fredrickson,<sup>14</sup> in a group of 9 patients with gall bladder or common duct drainage, showed that in 3 patients with biliary obstruction, but possessing normal livers, the total bile acid output, determined as glycocholic acid, reached the maximum output of approximately 2.0 Gm. per day about the fifth or sixth postoperative day. In those patients with cirrhotic livers or severe hepatitis and cholangitis the cholic acid output was less than 0.5 Gm. per day after two weeks of drainage. Ravdin and co-workers<sup>15</sup> studied liver bile obtained by means of a T-tube from 19 patients with complete common duct obstruction of a week's duration or more. In no case were bile acids present in the first specimens obtained, and generally bile acids, as determined by the Gregory-Pascoc method, first appeared from one to four weeks after release of the obstruction depending on the degree of liver damage and cholangitis. However, no attempt was made to correlate the duration of obstruction with the return of bile acids in the bile. Gray and co-workers,<sup>16</sup> in a group of 50 patients with T-tube drainage of the common duct, because of occlusion, found that in 21 cases with a "normal" liver, diagnosed by inspection, the concentration of bile acids gradually reached a fixed level of 2.0 Gm. per 100 c.c. of bile on the fifteenth to the twenty-first days. In 29 patients who showed varying degrees of liver damage, classified as mild to severe, the bile acid concentration ranged from 1.1 to 0.1 Gm. per 100 c.c. respectively, on the fifteenth day. Greene and co-workers,<sup>17</sup> in a recent report, found in 25 patients with apparently "normal" livers, that the bile salt concentration of 800 mg. per cent was reached in five days after relief of common duct obstruction. In those cases with moderate or severe liver damage, the recovery was much slower and some of the severe cases never returned to normal during the period of drainage. Further, these investigators administered mixed bile salts to the patients in their series and found that this treatment had no effect on the concentration of bile salts in the fistula bile but did markedly improve the clinical condition of their patients, a fact which we have noted in a large number of our biliary fistula dogs suffering from partial obstruction or hepatitis.

In our series of twenty animals in which release of common duct obstruction was performed seven days after the occlusion of the duct, the total daily cholic acid output returned to normal in approximately

five days. In two dogs, Nos. 5 and 7 of the control group, the cholic acid recovery occurred only after ten and nine days, respectively. These animals refused to eat during the early postoperative period and only began to eat about one week after the operation. Two animals in the bile-salt series, Nos. 6 and 7, had low cholic acid outputs of 896 and 782 mg. per day, which can be attributed to the fact that these animals ate very little during the recovery period. Thus, anorexia and diet are important factors in the recovery of cholic acid output after relief of biliary obstruction. Greene and associates<sup>17</sup> have reported that the administration of large amounts of dextrose by venoclysis improved the bile salt secreting function of the liver. Further, our results and those of Greene and co-workers<sup>17</sup> show that the administration of bile salts was not efficacious in increasing the concentration or total daily output of bile acids in fistula bile. We used large amounts of a potent choleric, 3 Gm. of ketocholanic acid daily, since we believed that a brisk choleresis would "flush out" the biliary passages and thus tend to aid in the recovery of the liver. It must be kept in mind, however, that a severely diseased liver can secrete copious quantities (cholerrhagia<sup>18</sup>) of a highly pigmented bile which contains little or no bile salts, or can secrete a pigmented bile which contains no bile salts.

#### SUMMARY AND CONCLUSIONS

We have studied the effect of bile salt administration on (1) the elimination of bile pigment from the blood and urine, and (2) the recovery of cholic acid after release of common duct obstruction. Jaundice was produced in twenty dogs by doubly ligating the common bile duct and resecting a portion of the duct. After seven days of complete obstruction, the animals were converted into biliary fistula dogs according to the Roux-McMaster method. One group of ten animals was fed bile salts while the other group of ten animals served as a control. Three-gram daily doses of ketocholanic acid (ketochol) during the postoperative recovery period did not increase the rate of removal of the excess bile pigment from the blood and urine. In both groups the pigment disappeared from the blood and urine in approximately five days. The normal total cholic acid output of approximately 1.2 Gm. per day occurred, in both groups, on the average, five days after release of the common duct obstruction. It was found that the early return of pre-operative eating habits was an important index of the recovery of cholic acid; whereas, the administration of bile salts seemed to play a minor role in improving the bile salt secreting function of the liver. Since we have found previously that the administration of bile salts to animals with complete obstruction of the common bile duct does not affect longevity and does no apparent harm,<sup>19</sup> the administration of bile salts in the presence of a damaged liver is not contraindicated.

## REFERENCES

1. Boyce, F. F.: Hepatic and Biliary Tract Disease, *Ann. Surg.* 109: 351, 1939.
2. Boyce, F. F., and McFetridge, E. M.: Studies of Hepatic Function by the Quick Hippuric Acid Test. I. Biliary and Hepatic Disease, *Arch. Surg.* 37: 401, 1938.
3. Finsterer, H.: Surgical Treatment of Acute Cholecystitis and Common Duct Obstruction, *SURGERY* 6: 491, 1939.
4. Appel, B.: Sodium Dihydrocholate in Arspenamine Poisoning, *Arch. Dermat. & Syph.* 27: 401, 1933.
5. Appel, B., and Jankelson, I.: Treatment of Arsenical Hepatitis With Sodium Dihydrocholate; Experimental and Clinical Studies in Cases of Arspenamine Poisoning, *Arch. Dermat. & Syph.* 32: 422, 1935.
6. Berman, A. L., Snapp, E., and Ivy, A. C.: The Effect of Choleresis on the Rate of Excretion of Intravenously Injected Bilirubin, *Am. J. Physiol.* 132: 176, 1941.
7. Gibson, R. B., and Goodrich, G. E.: Determination of Plasma Bilirubin: A Modified van den Bergh Procedure, *Proc. Soc. Exper. Biol. & Med.* 31: 413, 1934.
8. Rous, P., and McMaster, P. D.: A Method for the Permanent Sterile Drainage of Intraabdominal Ducts as Applied to the Common Duct, *J. Exper. Med.* 37: 11, 1923.
9. Berman, A. L., Snapp, E., Ivy, A. C., Atkinson, A. J., and Hough, V. H.: The Effect of Various Bile Acids on the Volume and Certain Constituents of Bile, *Am. J. Digest. Dis.* 7: 333, 1940.
10. Reinhold, J. G., and Wilson, D. W.: The Determination of Cholic Acid in Bile, *J. Biol. Chem.* 96: 637, 1932.
11. Dragstedt, C. A., and Mills, M. A.: The Removal of Intravenously Injected Bilirubin From the Blood Stream in the Dog, *Am. J. Physiol.* 119: 713, 1937.
12. Mills, M. A., and Dragstedt, D. A.: Removal of Intravenously Injected Bromsulphthalein From the Blood Stream of the Dog, *Arch. Int. Med.* 62: 216, 1938.
13. Bollman, J. L., and Mann, F. C.: The Influence of the Liver in the Formation and Destruction of Bile Salts, *Am. J. Physiol.* 116: 214, 1936.
14. Greene, C. H., Walters, W., and Fredrickson, C. H.: The Composition of the Bile Following the Relief of Biliary Obstruction, *J. Clin. Investigation* 9: 295, 1930-31.
15. Ravdin, I. S., Johnston, C. G., Riegel, C., and Wright, S. L.: Study of Human Liver Bile After Release of Common Duct Obstruction, *J. Clin. Investigation* 12: 659, 1933.
16. Gray, H. K., McGowan, J. M., Nettraur, W. S., and Bollman, J. L.: Hepatic Damage in Biliary Disease, *Arch. Surg.* 37: 790, 1938.
17. Greene, C. H., Carter, R. F., Hotz, R., and Twiss, J. R.: The Post-operative Concentration of Bile Salts in Human Bile, *Am. J. Surg.* 49: 264, 1910.
18. Walters, W., and Parkam, D.: Renal and Hepatic Insufficiency in Obstructive Jaundice, *Surg. Gynec. & Obst.* 35: 605, 1922.
19. Berman, A. L., Grodins, F. S., and Ivy, A. C.: Bile Salts and Obstructive Jaundice, *Proc. Soc. Exper. Biol. & Med.* In press.

# BLOOD STUDIES DURING ANESTHESIA

## REFERENCE TO INFECTIONS AND NONINFECTIONS

J. D. MARTIN, JR., M.D., AND ROY ROBERTSON, B.S., ATLANTA, GA.

*(From the Department of Surgery, Emory University School of Medicine)*

MANY factors are involved in the causation of convulsions during anesthesia. Primarily the condition of the patient and the nature of the anesthetic agent are directly concerned with each occurrence. There have been noted various phenomena which are coincident with these convulsive seizures; namely, overdosage of the anesthetic, encephalopathy with nitrous oxide, impurities in the anesthetic agent, acute toxemia with associated hyperpyrexia, ether diathesis, excessive carbon dioxide, anoxia, overdosage of atropine, and numerous others.<sup>1</sup> The majority of the reported convulsions have been associated with severe infections, although they may occur in cases with no infection and during anesthetics of short duration.

Considerable experimentation has been performed by other workers concerning the blood changes during anesthesia. The majority of these studies were conducted during ether anesthesia. A recent study by Fay and others<sup>2</sup> has shown that base bound by protein is decreased significantly during one hour of ether anesthesia. Several investigators<sup>3-4</sup> have reported a depression of serum calcium during anesthesia with ether. McAllister<sup>5</sup> found that administration of this agent for one hour in operative patients caused an average drop in plasma volume of 11 per cent. This loss, when calculated from the rise in plasma protein, was 9.3 per cent. Further evidence is presented by Searles,<sup>6</sup> showing that cell volume, platelets, and erythrocytes were increased during ether anesthesia. This was attributed to hyperventilation with increased water loss and to a contraction of the spleen, forcing more red blood cells into the general circulation. Splenectomy reduced this change by approximately one-half.

Anesthesia by intravenous injection of barbiturates has been shown to produce little alteration in the blood constituents. Bourne and co-workers<sup>7</sup> found a lowered pH, decreased carbon-dioxide combining power, and hydremia. Searles<sup>8</sup> and Higgins and Corwin<sup>9</sup> reported a lowering of the specific gravity of the blood during amytal anesthesia in animals. This was shown to be due to a dilatation of the spleen, with an erythrocytic influx from the circulating blood. Hydration of the blood has been noted by Bollman and associates.<sup>10</sup>

Peritonitis produces changes in the blood which are referable to dehydration, destruction of protein incident to infection and toxemia, and alkalemia from a chloride loss by vomiting. Orr and Haden<sup>11</sup> found an

early drop in chloride concentrations occurring with experimental peritonitis in dogs. They report also a rise in urea and nonprotein nitrogen with inconstant variations in the carbon-dioxide combining power of the plasma. In those cases in which alkalosis becomes well established, there is a simultaneous rise in the combining power of the plasma for carbon dioxide.

In the light of previous investigations and prompted by the occurrence in two operative patients of typical anesthetic convulsions, the following studies were carried out. An attempt was made to determine in both the operative patient and the experimental animal the changes, incident to anesthesia, in blood concentration, plasma water, plasma protein, and the available ionic serum calcium.

#### MATERIALS AND METHODS

*Part I. Surgical Cases.*—Blood studies were performed on operative patients in the University Hospitals. Samples were obtained preoperatively, during the course of the anesthesia, and at the conclusion of the operation. The cases were those admitted with acute septic processes. Essentially, these consisted of local or general peritonitis resulting from perforated gangrenous appendicitis. Studies of the blood were also carried out during anesthesia for noninfected conditions. In this manner there was formed a control series for this group.

*Part II. Experimental.*—Blood examinations similar to the above were conducted on the dog: An attempt was made to parallel the state seen in the control cases in Part I. Production of peritonitis with subsequent observation of the blood during anesthesia was carried out. In these experiments the animals were anesthetized by two methods: (a) A 6.4 per cent solution of sodium pentobarbital (nembutal) was injected intravenously, in the proportion of 64 mg. of drug per 5 pounds of body weight. (b) Ether was administered by the open-drop method, with an attempt to secure complete anesthesia with a minimum of excitement in the animal.

Peritonitis was produced by the following methods:

*A. Bacterial Injections.*—Intraperitoneal injections of a virulent strain of *B. coli*, grown on twenty-four hour plain agar slants and suspended in 6 per cent gum acacia solution or 12 per cent mucin solution,<sup>11</sup> were given. Ten cubic centimeters of the acacia solution, containing approximately one billion organisms per cubic centimeter, was injected. Five cubic centimeters of the mucin solution was given. This contained approximately five hundred million bacteria per cubic centimeter. Each of these methods produced peritonitis of varying severity within eighteen to forty-eight hours.

*B. Aseptic Peritonitis.*—Aseptic peritonitis was produced by the method of David<sup>12</sup> by intraperitoneal injections of 15 per cent turpentine-water emulsion. One cubic centimeter of the emulsion was used per kilogram of body weight. This method produced fibrinous peritonitis

with transudate within forty-eight hours. Best results were obtained after two consecutive injections twenty-four hours apart.

*C. Perforation Peritonitis.*—This was produced by ligation of the appendix and its mesentery. In a few instances, the descending colon was perforated or a portion of the mesentery of the ileum ligated. All of the above operative procedures resulted within forty-eight to seventy-two hours in a progressive fatal peritonitis in approximately 60 per cent of the animals. In those surviving, there was a local peritonitis or a less active generalized nonfatal infection. Confirmation autopsies were performed.

Normal blood samples were obtained on all dogs before peritonitis was produced. A specimen was taken at the height of the infection. The dog was then anesthetized and samples were drawn at hourly intervals for two or three hours. The control animals were similarly anesthetized, a normal sample obtained as soon as deep anesthesia was reached, and at hourly intervals for two or three hours.

Examinations of the blood of the operative cases and experimental animals were in most instances conducted as follows. Each sample was divided into two 1 c.c. portions, to each of which was added 1 mg. of heparin, and a 12 c.c. portion which was allowed to clot for serum. Evaporation was prevented by sealing the tubes immediately after the blood was taken. The two smaller samples were used in the determination of the specific gravity of the whole blood and plasma. The falling drop method of Barbour and Hamilton was employed.<sup>13</sup> Total serum calcium was determined by the Clark-Collip modification of the Kramer-Tisdall method.<sup>14</sup> Plasma protein was calculated from the plasma specific gravity according to the formula of Moore and Van Slyke.<sup>15</sup> Ionized calcium concentrations were then read to the nearest tenth of a milligram from the nomogram adapted for clinical use by McLean and Hastings.<sup>16</sup> The ionic calcium fraction varies directly as the total concentration, and indirectly with protein content of the plasma, and if these two are known for any plasma sample, calculations can be made from their nomogram, calibrated by the frog heart method.

#### DISCUSSION

It is an established clinical fact that anhydremia, from water loss or deprivation, results in concentration of the blood with an equivalent or nearly equivalent increase of its formed elements and chemical constituents. Hydremia produces a similar proportionate decrease in blood constituents.

In the experimental animal this proportionate change was not found in peritonitis, either before or during anesthetization. With the development of peritonitis there was noted an average decrease in serum calcium of 0.4 mg. (Figs. 3 and 4). This diminution in calcium, although closely approximating the limits of variation for the chemical determination, appears to be significant in the light of the expected rise incident to

hemocoeonecentration, shown by an elevated specific gravity of whole blood and plasma. Ionized calcium fractions diminished with the fall in the total amount. Approximately 80 per cent of the entire group of peritonitis cases show such a decrease. The variable results in the remaining number are perhaps explained by the multiplicity of factors involved in the production of experimental peritonitis; namely, the time element (some infections developing within twenty-four to forty-eight hours, others requiring three to five days), variations in the amount of fluids consumed, degrees of infection present, and others.

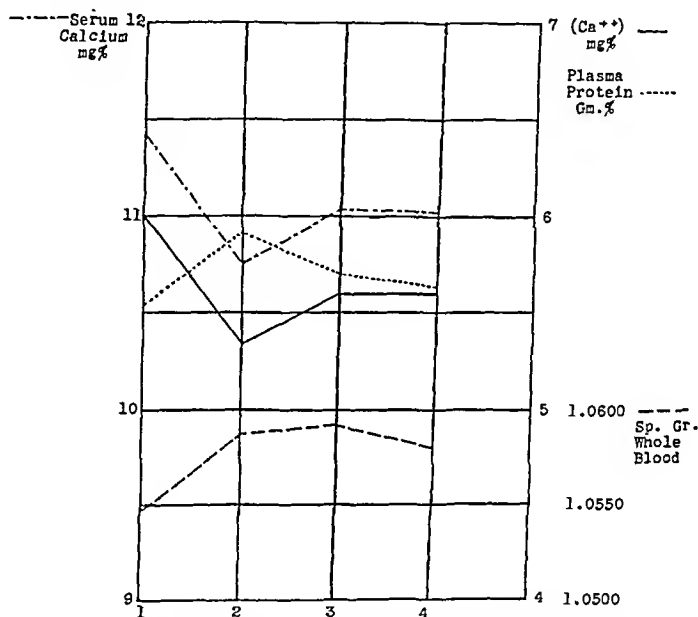


Fig. 1.—Composite graphs of controls, ether anesthesia. 1, Pre-experimental sample; 2, after one hour of anesthesia; 3, after two hours of anesthesia; 4, after three hours of anesthesia.

In the control dog, ether anesthesia produced an increased water loss. Moreover, calcium decreased, instead of increasing proportionately with the blood protein in the process of dehydration. An average fall in calcium of 0.7 mg. is observed during the first hour (Fig. 1). At the end of three hours the total amount had not reached its original level. Ionized concentrations were lowered with the total calcium. The change in the ionized portion was a result of the simultaneous decrease of the total amount and the rise in the plasma protein.

Barbital anesthesia, by intravenous injection of sodium pentobarbital in dogs of the control group, did not produce the progressive depression of ionized calcium as did ether. With the use of this anesthetic there occurred hydration of the blood, with a resultant hemodilution. This can be explained partly by an increased splenic reserve of red blood cells and partly as being due to an action inherent in the pharmacodynamics of the drug itself. This latter action is observed as an increase in plasma

water, as shown by the progressive fall of plasma protein concentrations. (Fig. 2.) The diminution in calcium was apparently proportional to the degree of hydration and is evidenced by the fixed ionic calcium concentrations during the two-hour period.

The administration of ether for a period of one hour to dogs with peritonitis caused a further depression of the total serum calcium, an average of 0.64 mg. (Fig. 3). The decreases in the ionized fractions, initiated by falling total concentrations, were aided by the rising protein content. The end of two hours of anesthesia was marked by no further variation in total calcium, and only a slight rise in ionic calcium, resulting from a decrease in protein. This latter decrease shows a return of water into the plasma, in spite of the continued increase of whole blood specific gravity.

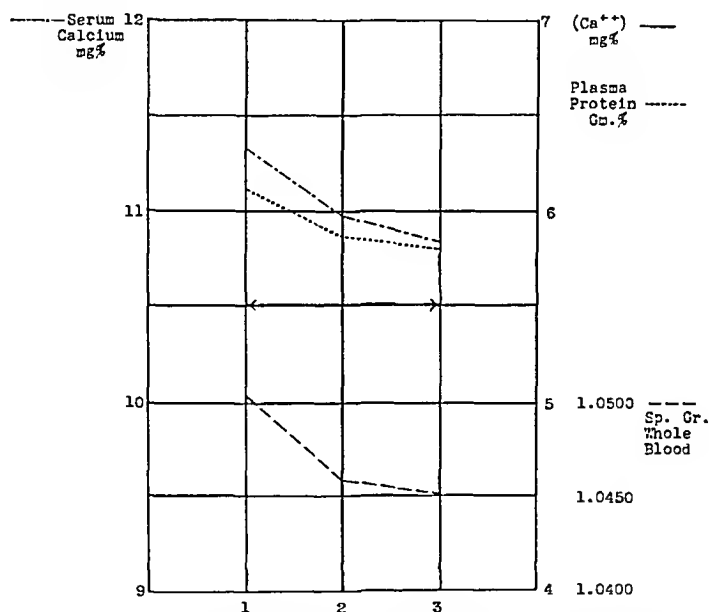


Fig. 2.—Composite graphs of controls, nembutal anesthesia. 1, Pre-experimental sample; 2, after one hour of anesthesia; 3, after two hours of anesthesia.

In the peritonitis group given intravenous anesthesia, the progressive fall in total serum calcium was observed. At the end of one hour little change is noted in total calcium, and a rise in the ionic fraction is apparent. This is explainable by an increase in plasma water, reducing the protein concentration and consequently releasing more calcium in the ionized form. It has been shown that barbiturate anesthesia in dogs produces a fall in rectal temperature of two to three degrees.<sup>7</sup> This change, best shown during the second hour of anesthesia, resulted in hemoconcentration and an increased whole blood specific gravity. The concentration observed in this infected group appeared to be of greater magnitude than that seen in the controls and overshadowed the hemo-



dilution usually apparent with this anesthesia. By two hours, total calcium had fallen markedly, but protein concentration remained rather constant. Ionized calcium, rising at one hour, diminished by the end

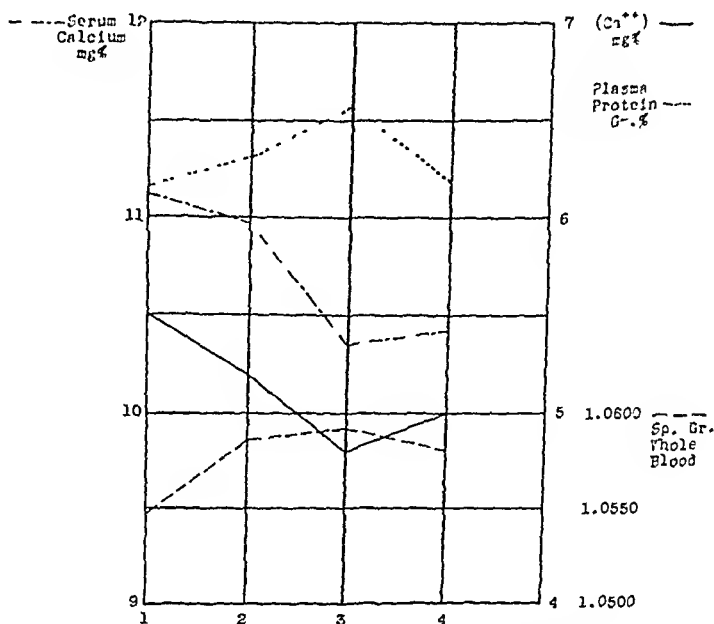


Fig 3—Composite graphs of peritonitis, ether anesthesia. 1, Pre-experimental sample; 2, height of infection, just before anesthesia was given, 3, after one hour of anesthesia, 4, after two hours of anesthesia

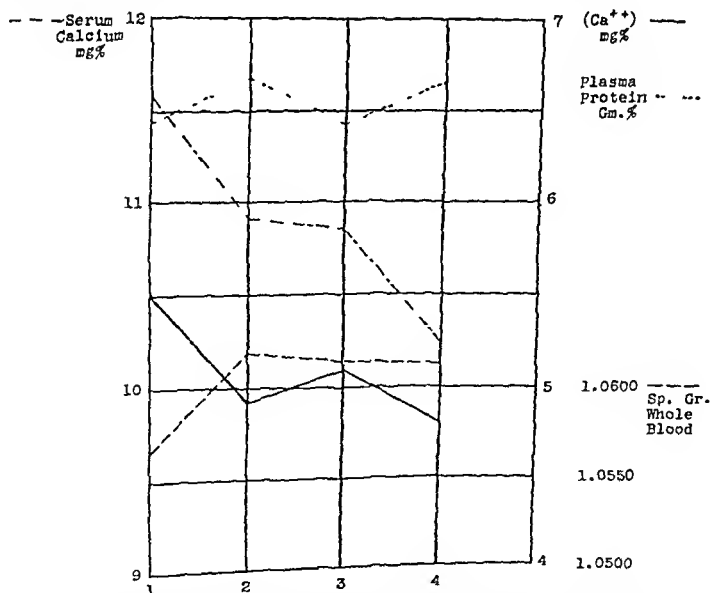


Fig 4—Composite graphs of peritonitis, nembutal anesthesia. 1, Pre-experimental sample, 2, height of infection, just before anesthesia was given, 3, after one hour of anesthesia, 4, after two hours of anesthesia

of the second hour, concurrently with the fall in the total amount. It will be noted that these results do not parallel those in the group of controls (Fig. 2).

The above findings in the experimental animal group were essentially substantiated in the blood studies on the operative patient. A total of 27 patients were observed, of whom 16 had ether anesthesia and 11 cyclopropane. Each of these groups was further subdivided into the noninfected cases, comprising the controls, and those with septic processes.

The control cases, given cyclopropane anesthesia, exhibited an average drop of 1 mg. in total serum calcium during the operative procedure, with a gain of 0.6 mg. at the conclusion of the operation. The cases with infection, however, showed a progressive drop in total serum calcium, an average of 0.4 mg. during the procedure, with an additional decrease of 0.3 mg. by the end of the anesthesia. In all cases, the degree of the depression of the calcium seemed to depend upon the length of the anesthesia. The average length in this series was forty-five minutes.

In the group with ether anesthesia similar changes were noted. The control cases exhibited an average decrease in total serum calcium of 0.75 mg. and in ionic calcium of 0.1 mg. during the time required for operative procedures. Those patients with sepsis were shown to have an average fall of 0.8 mg. in total calcium and of 0.3 mg. in the ionized fraction, during the time for operative procedures. The rather marked changes that occurred in some of these patients are exemplified by the findings in Case 2. Here the preoperative total calcium level was 11.90 mg., the midoperative sample 10.20 mg., and at the conclusion of the anesthesia, 9.94 mg. per cent, a total drop of nearly 2 mg. This patient had acute gangrenous appendicitis, with local peritonitis. In Patient H. P., acute cholecystitis requiring cholecystectomy, an ether anesthesia of one hour and fifteen minutes' duration caused a fall in calcium (total) from 11.80 mg. to 10.05 mg. per cent, a decrease of 1.75 mg.

In view of the fact that the above averages in hospital cases do not present the striking results seen in the experimental animal, it should be pointed out that with these patients the anesthetics were of shorter duration and the processes less acute. The calcium depression, noted clinically, is substantiated by the more carefully controlled experimental work with animals.

#### SUMMARY

There is probably no individual factor or single group of factors responsible for the production of convulsive seizures during anesthesia. It is realized that conditions vary widely with each patient, and that in any convulsion one or more groups of diverse factors or any combination of these may be responsible.

Observations during convulsions in operative patients have been made by other investigators. In the majority of cases the convulsions oc-

curred in the presence of severe sepsis and near the termination of the anesthesia. In many instances, the control of the seizure was effected by administration of a calcium salt intravenously.

This study consists of examination made upon the blood of operative patients and experimental animals during anesthesia, both in the normal state and in the presence of sepsis. Studies of the amount of available calcium and degree of dehydration and hydration of the blood were carried out.

It has been found that the available ionic calcium in the blood is decreased during ether anesthesia. The duration of the anesthesia apparently determines the degree of lowering of the calcium level.

Acute abdominal infections effect a decrease in ionized calcium in both the operative patient and experimental animal. This change is further augmented during anesthetization with ether.

The use of intravenous sodium pentobarbital does not significantly affect the ionic calcium levels in the control or septic state.

In no instance, either experimentally or clinically, was there noted a lowering of the calcium levels to within the limits of those seen in tetany.

#### REFERENCES

1. Lundy, J. S.: Convulsions Associated With General Anesthesia, *SURGERY* 1: 666-687, 1937.
2. Fay, M., Andersch, M., and Kenyon, M. B.: Blood Studies Under Anesthesia. I. Ether Administered to the Dog by Open Drop and in a Closed System, *J. Pharmacol. & Exper. Therap.* 66: 224-233, 1931.
3. Marenzi, A. D., and Gerschman, R.: Variations in the Inorganic Constituents of the Plasma During Ether Anesthesia, *Compt. rend. Soc. de biol.* 114: 1226-1228, 1933.
4. Lipow, E., Weaver, W. K., and Reed, C. I.: Effects of Ether Anesthesia on the Inorganic Constituents of the Blood, *Am. J. Physiol.* 90: 432-433, 1929.
5. McAllister, F. F.: The Effect of Ether Anesthesia on the Volume of Plasma and Extracellular Fluid, *Am. J. Physiol.* 124: 391-397, 1938.
6. Searles, P. W.: The Effect of Ether and Sodium Amytal Anesthesia on the Blood, *Am. J. Surg.* 41: 399-404, 1938.
7. Bourue, W., Bruger, M., and Dreyer, N. B.: The Effects of Sodium Amytal, *Surg., Gynec. & Obst.* 51: 356-360, 1930.
8. Higgins, G. M., and Corwin, W. C.: The Effect of Splenectomy on the Number of Erythrocytes and Leukocytes in the Peripheral Blood of Rats and Rabbits Under Ether and Sodium Amytal Anesthesia, *SURGERY* 1: 703-710, 1937.
9. Bollman, J. L., Svrbely, J. L., and Mann, F. C.: Blood Concentration Influenced by Ether and Amytal Anesthesia, *SURGERY* 4: 881-886, 1938.
10. Orr, T. G., and Haden, R. L.: Treatment of Experimental Acute General Peritonitis in the Dog With Ileostomy and Sodium Chloride Solution, *J. Exper. Med.* 49: 526-530, 1929.
11. Seley, G. P.: Peritonitis in Cats Produced by Intraperitoneal Injections of *Bacillus Coli*, Suspended in Mucin, *Arch. Surg.* 39: 783-791, 1939.
12. David, V. C.: Peritonitis: An Experimental Study, *Surg. Gynec. & Obst.* 45: 287-293, 1927.
13. Barbour, H. G., and Hamilton, W. F.: The Falling Drop Method for Determining Specific Gravity, *J. Biol. Chem.* 69: 625-640, 1926.
14. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Calcium With a Suggested Modification, *J. Biol. Chem.* 63: 461-464, 1925.
15. Moore, N. S., and Van Slyke, D. D.: The Relationship Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, *J. Clin. Investigation* 8: 337-355, 1930.
16. McLean, F. C., and Hastings, A. B.: Clinical Estimation of Calcium-Ion Concentrations in the Blood, *Am. J. M. Sc.* 189: 601, 1935.

# DYNAMIC CHANGES IN EXPERIMENTAL PULMONARY EMBOLISM\*

R. S. MEGIBOW, M.D., L. N. KATZ, M.D., AND F. S. STEINITZ, M.D.,  
CHICAGO, ILL.

(From the Cardiovascular Department, Michael Reese Hospital)

## INTRODUCTION

AN EXTENSIVE literature has accumulated dealing with the hemodynamic changes and the mechanism of death following clinical and experimental pulmonary embolism. This has been adequately reviewed in the past (Mendlowitz,<sup>1</sup> de Takats,<sup>2</sup> Horn<sup>3</sup>). These studies suggest that pulmonary embolism is followed by an elevation in pulmonary arterial pressure. Clinically, however, such evidence is inferential, no method being as yet available to record the pulmonary pressure in man. Experimentally, direct determinations of the pulmonary arterial pressure have not been made in normal anesthetized or unanesthetized animals. The latter would permit a correlation with other circulatory changes and would make possible a better evaluation of the ensuing circulatory adjustments. In addition such studies would help in determining the evolution of the various changes leading to death and would thus help in establishing the therapeutics on fundamental physiologic principles. Such a method is now available<sup>4-6</sup> and the perfection of technique in its use in our laboratory<sup>7</sup> has led us to reinvestigate the dynamic changes following experimentally produced pulmonary embolism.

## METHODS

The technique of applying the cannula about the pulmonary artery<sup>7</sup> consists essentially in the application, under strictest asepsis, of a specially designed silver cannula around the pulmonary artery by an exposure through the third or fourth left intercostal space. The incision is closed tightly in layers, all the air entrapped in the pleural cavity removed and the dog is then allowed to recover.

In an attempt to simulate as closely as possible the syndrome of clinical pulmonary embolism, observations have been carried out in three types of preparations, namely: (1) With an embolus composed of Penrose tubing filled with fluid, similar in all respects to that described by Mendlowitz.<sup>1</sup> This is analogous to clinical involvement of the main pulmonary artery or its two major divisions. (2) With emboli composed of pea seeds, prepared and administered according to the method of Binger, Brow, and Branch.<sup>8</sup> This is the counterpart of multiple

\*Aided by the A. D. Nast Fund for Cardiac Research and the Otto Baer Fund.  
Received for publication, March 20, 1941.

clinical embolism of the moderately sized radicles of the pulmonary arteries. (3) With emboli composed of starch granules suspended in saline solution prepared and administered, except for a more rapid injection rate and larger dosage, according to the method of Binger and co-workers.<sup>9</sup> This simulates multiple clinical embolism of the pulmonary arterioles and capillaries.

Fourteen dogs were used in this study. One week following insertion of the pulmonary cannula, the animal was prepared for the type of embolus desired. Both before and at frequent intervals following induction of pulmonary embolism, simultaneous pulmonary and systemic arterial blood pressures were obtained using the Hamilton needle manometer,<sup>10</sup> according to the technique previously described by us.<sup>11</sup> Arterial pulse wave contours were obtained at fast camera speeds to demonstrate that the needles were within the arterial lumina. Systemic venous pressure was recorded by a water manometer from one of the superficial veins of the forelimb. The respiratory rate was determined by actual count over one minute, while the heart rate was determined from the optically recorded pressure curve.

It was possible to follow the changes after the passage of the "Mendlowitz embolus" in the unanesthetized dog, the right external jugular vein needed for the insertion of the embolus being exposed under local (procaine hydrochloride) anesthesia. On the other hand, in the experiments with pea seeds and starch granules, anesthesia was required because of the restlessness and excitement induced by the embolism in the dogs. The animals, therefore, were kept lightly anesthetized with nembutal intravenously. Subsequent studies of ours have shown that the dynamics following embolism are little if at all altered by general anesthesia.

Autopsies were performed to note the position of the emboli as well as the effect upon the heart, lungs, and other viscera, and in the starch granule experiments the extent and degree of occlusion of the pulmonary arterioles and capillaries were estimated microscopically.

#### RESULTS

A characteristic experiment for each type of embolism is summarized in Tables I, II, and III.

I. *Controls*.—Since the "Mendlowitz embolus" is forced into the circulation by the injection of 100 to 150 c.c. of normal saline solution, and as much as 200 c.c. of saline solution is employed in the starch emboli experiments, the changes evoked by rapid fluid administration were accordingly studied for purposes of control in two unanesthetized dogs by injecting 150 c.c. of normal saline solution in fifteen seconds through a No. 13 needle inserted into the right external jugular vein. The injection was followed by a transient rise in systolic pulmonary and systemic pressures lasting ten to fifteen minutes, respiration and heart rate

TABLE I  
MENDLOWITZ EMBOLUS\*

	CON- TROL	150 c.c. saline solution intravenously	IMME- DI- ATELY AF- TER FLUID INJECTED	AFTER 15 MIN.	Embolus passed down vein		10 MIN. AFTER EMBOLUS WAS PASSED	20 MIN. AFTER	25 MIN. AFTER	30 MIN. AFTER	1 HR. AFTER	1 HR. 15 MIN. AFTER	3 HR. AFTER	5 HR. AFTER	Dogs died; extreme dyspnea with gasp- ing respiration
Pulmonary arterial pres- sure, mm.Hg	30/5		40/5	30/5			65/10	48/10	60/10	70/10	55/10	50/10	52/15	55/15	
Systemic arterial pres- sure, mm.Hg	120/70		140/75	130/75			150/85	160/100	120/70	150/100	120/70	130/80	120/65	125/75	
Systemic venous pressure, cm.H <sub>2</sub> O	5							7					10	15	
Heart rate/min.	156		156	156			168	168	168	168	192	192	204	192	
Respiratory rate/min.	22		26					42		40		48	42	46	

\*Necropsy, riding embolus of pulmonary artery.

clinical embolism of the moderately sized radicles of the pulmonary arteries. (3) With emboli composed of starch granules suspended in saline solution prepared and administered, except for a more rapid injection rate and larger dosage, according to the method of Binger and co-workers.<sup>9</sup> This simulates multiple clinical embolism of the pulmonary arterioles and capillaries.

Fourteen dogs were used in this study. One week following insertion of the pulmonary cannula, the animal was prepared for the type of embolus desired. Both before and at frequent intervals following induction of pulmonary embolism, simultaneous pulmonary and systemic arterial blood pressures were obtained using the Hamilton needle manometer,<sup>10</sup> according to the technique previously described by us.<sup>11</sup> Arterial pulse wave contours were obtained at fast camera speeds to demonstrate that the needles were within the arterial lumina. Systemic venous pressure was recorded by a water manometer from one of the superficial veins of the forelimb. The respiratory rate was determined by actual count over one minute, while the heart rate was determined from the optically recorded pressure curve.

It was possible to follow the changes after the passage of the "Mendlowitz embolus" in the unanesthetized dog, the right external jugular vein needed for the insertion of the embolus being exposed under local (procaine hydrochloride) anesthesia. On the other hand, in the experiments with pea seeds and starch granules, anesthesia was required because of the restlessness and excitement induced by the embolism in the dogs. The animals, therefore, were kept lightly anesthetized with nembutal intravenously. Subsequent studies of ours have shown that the dynamics following embolism are little if at all altered by general anesthesia.

Autopsies were performed to note the position of the emboli as well as the effect upon the heart, lungs, and other viscera, and in the starch granule experiments the extent and degree of occlusion of the pulmonary arterioles and capillaries were estimated microscopically.

## RESULTS

A characteristic experiment for each type of embolism is summarized in Tables I, II, and III.

*I. Controls.*—Since the "Mendlowitz embolus" is forced into the circulation by the injection of 100 to 150 c.c. of normal saline solution, and as much as 200 c.c. of saline solution is employed in the starch emboli experiments, the changes evoked by rapid fluid administration were accordingly studied for purposes of control in two unanesthetized dogs by injecting 150 c.c. of normal saline solution in fifteen seconds through a No. 13 needle inserted into the right external jugular vein. The injection was followed by a transient rise in systolic pulmonary and systemic pressures lasting ten to fifteen minutes, respiration and heart rate

TABLE III  
STARCH GRANULE EMBOLI

	CON- TROL	15 MIN.*	30 MIN.*	40 MIN.*	1 HR. 5 MIN.*	1 HR. 15 MIN.*	1 HR. 20 MIN.*	1 HR. 35 MIN.*	1 HR. 45 MIN.*	1 HR. 55 MIN.*
Pulmonary arterial pressure, mm.Hg	32/15	10/20	12/22	17/30	50/30	65/37	90/50	90/50	90/20	
Systemic arterial pressure, mm.Hg	150/85	140/75	135/70		150/80	160/95	160/75	175/100	140/80	
Systemic venous pressure, cm.H <sub>2</sub> O	7			15			24		11	Dog died
Heart rate/min.	96	96	120	144		132	168	168	192	V.F.†
Respiratory rate/ min.	20	28	28	36	52	61	80	101	120	Extreme tachypnea

\*After injection of first starch solution.

†Ventricular fibrillation.



TABLE II  
PEA SEED EMBOLI

	CON- TROL	5 MIN.*	7 MIN.*	11 MIN.*	17 MIN.*	19 MIN.*	27 MIN.*	30 MIN.*	34 MIN.*	38 MIN.*	41 MIN.*	48 MIN.*	50 MIN.*
Pulmonary arterial pressure, mm.Hg	21/6	31/6	33/8	44/13	57/15	65/18		70/20	75/25	80/25		50/25	25/2
Systemic arterial pressure, mm.Hg	125/70	125/70	120/60	175/85	125/75	155/80		130/60	175/85	170/75		115/50	85/40
Systemic venous pressure, mm.Hg	6		5				7				9		
Heart rate/ min.	144	180	168	168	156	156		156	168	144		144	12
Respiratory rate/min.	43	80		72	86	100	88	102	100	120		16	9
		9 peas injected intravenously	3 peas injected intravenously		5 peas injected intravenously	3 peas injected intravenously		5 peas injected intravenously	5 peas injected intravenously	10 peas injected intravenously		5 peas injected intravenously	5 peas injected intravenously

\* After injection of first pea seeds

Dyspnea and moderate tachypnea were noted usually coincidentally with the rise in pulmonary arterial pressure. The changes in respiration tended to become progressively more severe, until terminally when respiration usually slowed markedly and became gasping in character. Cyanosis appeared at some variable time after embolism and when once apparent it progressively intensified.

Tachycardia followed embolism in 2 dogs; presumably terminal ventricular fibrillation superseded the sinus mechanism in 1 of these animals. In the other 2 animals the changes in rate were minimal, except that terminally the rate slowed in 1 of them.

### *III. Effect of Minor Multiple Pulmonary Embolism.—*

A. MULTIPLE EMBOLISM OF MODERATELY SIZED ARTERIES.—At autopsy, in the 4 dogs in which pea-seed embolism was studied, the findings were similar to those described by Binger and associates.<sup>5</sup> The seeds were covered with fibrin and ante-mortem clot and appeared to have completely occluded the moderately sized branches of the pulmonary artery. The lungs were characteristically pale containing minimal quantities of blood while the right heart was constantly dilated.

The mode of seed administration varied in the different animals. Two dogs received a total dose of twenty peas at one time, while the other 2 dogs received thirty-five and fifty pea seeds in divided doses, respectively. The characteristic response to seed embolism was an abrupt rise in systolic and diastolic pulmonary pressures. Whether administered in single or divided doses, pulmonary hypertension, once it appeared, became progressively more marked until terminally when, in the 3 animals in which readings were obtainable, the pulmonary pressure tended to fall rapidly toward zero. This would indicate that once a sufficient number of seeds have been administered to impose some resistance to blood flow through the pulmonary circuit, further elevations in pulmonary pressure become roughly quantitatively dependent upon increasing degrees of mechanical obstruction to the circulation through the pulmonary arteries. The progressive pulmonary hypertension noted following cessation of seed administration can therefore only be explained on the basis of increasing obstruction occasioned presumably by the addition of ante-mortem thrombi upon the pea seeds, or much less likely by a reflex pulmonary vasoconstriction.

The systemic arterial pressure, after fifteen to thirty minutes, rose moderately in 3 dogs. It then tended to fall to the control level and was so maintained until terminally when simultaneously with the pulmonary pressure it also declined rapidly. The venous pressure alterations in the pea-seed embolism were not striking; 2 dogs exhibited a slight rise, while the remaining dogs showed insignificant variations.

Changes in respiration occurred coincidentally with or soon after the appearance of pulmonary hypertension and consisted of progressive

remaining unchanged. (Table I.) The slight rise in systolic arterial pressure apparently is due to the increased output of the ventricle.

In two dogs in which the Mendlowitz embolus was used, autopsy revealed obstruction of the inferior and superior vena cava respectively. These dogs may therefore serve as further controls. In one of these animals the embolus was found lying in the cavity of the right auricle partially obstructing the inferior vena cava. No changes were noted in this animal over the three-hour period of observation. At the end of this time the dog was sacrificed and at autopsy the heart appeared grossly normal. In the other animal in which the embolus at autopsy was found lying partly within the superior vena cava and partly within the right auricle, no change in pulmonary pressure, systolic arterial pressure, or heart rate was observed. However, a slight increase in the rate and amplitude of respiration and a tremendous increase in the venous pressure were noted. The respiration gradually returned to normal, but the venous pressure remained elevated during the entire period measured. At autopsy, the heart and lungs appeared grossly normal. The obstruction was sufficient in this animal to have induced a superior vena cava syndrome.

II. *Effect of Major Pulmonary Embolism.*—Major pulmonary embolism using the Mendlowitz embolus was successfully induced in 4 dogs. In 2 of these dogs a riding embolus of the main pulmonary artery was found at necropsy and in the other 2 dogs a complete embolic occlusion of the right branch of the pulmonary artery had occurred. In all 4 animals the right heart appeared markedly dilated, while the coronary veins stood out distinctly and definitely overshadowed the coronary arteries. In 1 dog which died seven minutes after passage of the embolus, the lungs appeared pale and ischemic; in the remaining 3 dogs, in which death did not occur for periods of four to forty-eight hours, the lungs presented gross evidences of early pulmonary edema with focal areas of congestion. All 4 animals presented moderate to marked passive hyperemia of the liver. No other significant abnormalities were evident at necropsy.

The passage of the embolus was followed by an abrupt increase in both systolic and diastolic pulmonary pressures. The rise persisted with minor fluctuations throughout the period of observation. In 2 dogs a relatively small rise in systemic systolic and diastolic pressures occurred; in the other 2 no change was observed. After a variable period, the systemic arterial pressure tended to fall, reaching shock level in one dog. Venous pressure rose in the 3 animals in which it was measured. In 1 dog in which multiple readings were obtained, it was found that the elevation in venous pressure was gradual over a period of hours and occurred some time after the rise in pulmonary pressure. This would indicate the time lag necessary to induce a degree of venous distention great enough to record venous pressure elevation.

Dyspnea and moderate tachypnea were noted usually coincidentally with the rise in pulmonary arterial pressure. The changes in respiration tended to become progressively more severe, until terminally when respiration usually slowed markedly and became gasping in character. Cyanosis appeared at some variable time after embolism and when once apparent it progressively intensified.

Tachycardia followed embolism in 2 dogs; presumably terminal ventricular fibrillation superseded the sinus mechanism in 1 of these animals. In the other 2 animals the changes in rate were minimal, except that terminally the rate slowed in 1 of them.

### *III. Effect of Minor Multiple Pulmonary Embolism.—*

A. MULTIPLE EMBOLISM OF MODERATELY SIZED ARTERIES.—At autopsy, in the 4 dogs in which pea-seed embolism was studied, the findings were similar to those described by Binger and associates.<sup>5</sup> The seeds were covered with fibrin and ante-mortem clot and appeared to have completely occluded the moderately sized branches of the pulmonary artery. The lungs were characteristically pale containing minimal quantities of blood while the right heart was constantly dilated.

The mode of seed administration varied in the different animals. Two dogs received a total dose of twenty peas at one time, while the other 2 dogs received thirty-five and fifty pea seeds in divided doses, respectively. The characteristic response to seed embolism was an abrupt rise in systolic and diastolic pulmonary pressures. Whether administered in single or divided doses, pulmonary hypertension, once it appeared, became progressively more marked until terminally when, in the 3 animals in which readings were obtainable, the pulmonary pressure tended to fall rapidly toward zero. This would indicate that once a sufficient number of seeds have been administered to impose some resistance to blood flow through the pulmonary circuit, further elevations in pulmonary pressure become roughly quantitatively dependent upon increasing degrees of mechanical obstruction to the circulation through the pulmonary arteries. The progressive pulmonary hypertension noted following cessation of seed administration can therefore only be explained on the basis of increasing obstruction occasioned presumably by the addition of ante-mortem thrombi upon the pea seeds, or much less likely by a reflex pulmonary vasoconstriction.

The systemic arterial pressure, after fifteen to thirty minutes, rose moderately in 3 dogs. It then tended to fall to the control level and was so maintained until terminally when simultaneously with the pulmonary pressure it also declined rapidly. The venous pressure alterations in the pea-seed embolism were not striking; 2 dogs exhibited a slight rise, while the remaining dogs showed insignificant variations.

Changes in respiration occurred coincidentally with or soon after the appearance of pulmonary hypertension and consisted of progressive

dyspnea and tachypnea with an apparent increase in amplitude. Terminally, however, when the pulmonary and systemic arterial pressures began to fall rapidly, respiration slowed markedly and became stertorous. Increasingly severe cyanosis which became intense terminally was observed in all animals.

Changes in heart rate were inconstant. In 2 dogs progressive tachycardia developed, with the apparent advent of ventricular fibrillation terminally in 1 dog. In the remaining dogs variations in the cardiac rate were minimal until terminally when a marked bradycardia appeared with rates of 54 and 12 per minute. The exact nature of this bradycardia whether of sinus origin, or due to the development of complete or to partial A-V block, or to some other mechanism, was undetermined.

**B. MULTIPLE EMBOLISM OF PULMONARY ARTERIOLES AND CAPILLARIES.**—A 1:20 suspension of starch granules in distilled water was used in all 4 animals studied. Two dogs received a total dose of 50 c.c. of the suspension in one injection while the remaining 2 dogs received total amounts of 75 and 200 c.c. of the suspension, in divided doses.

At necropsy, the findings were essentially alike. The right heart appeared markedly dilated. The lungs were pale pink with no apparent gross edema fluid. Microscopically, however, small focal areas of congestion scattered throughout both lung fields were occasionally observed. In random sections, the granules appeared primarily to have occluded the arterioles, only an occasional granule being found bulging a capillary wall. Embolization was diffuse and extreme, practically all the pulmonary arterioles appearing to have been involved.

The pulmonary arterial pressure showed an abrupt rise in its systolic and diastolic levels. The elevation in pressure could be integrated with the increased pulmonary arteriolar resistance due to the mechanical obstruction by the starch granules in the arterioles, since repeated doses of the suspension produced further increments of pressure elevation. However, it was noted that one dog receiving a single dose of the suspension developed a further rise in pulmonary pressure after the initial elevation, possibly as a result of a gradual dispersion of the granules to previously nonoccluded arterioles or by reflex pulmonary arteriolar vasoconstriction. Terminally in 3 of the 4 dogs, the pulmonary pressure showed a moderate decline.

The systemic arterial pressure changes were not striking. This confirms similar observations by others.<sup>12-14</sup> However, an increase in pulse pressure and a fall in diastolic pressure such as has been reported by Binger and associates<sup>9</sup> was not observed. Noteworthy was the fact that in 1 dog each injection of starch suspension resulted in a slight fall in systemic pressure followed by a rapid return to the control level. Terminally in 1 dog the systemic pressure fell to shock levels. This fall coincided with a similar though less marked decline in pulmonary arterial pressure.

In contradistinction to Dunn<sup>12</sup> who observed no conspicuous venous pressure alteration we found that the venous pressure rose gradually in 3 dogs and fell in 1. This latter decline coincided with a fall in both the systemic and pulmonary arterial pressures. The data in this latter animal are significant since the pulmonary pressure was still found at mildly hypertensive levels when compared with the control readings at a time when a marked systemic arterial hypotension and a marked fall in venous pressure were present.

Coincident with the development of pulmonary hypertension, the rate of respiration increased. Once present, tachypnea progressively increased, being most marked at the time of death. In contradistinction to the labored, deepened, and more rapid respiration following major and seed embolism, the respiration following starch embolism was not labored and as the rate increased the amplitude appeared to decrease proportionally. During the period of tachypnea, cyanosis constantly developed and in all instances became intensified terminally.

In the 2 dogs in which the heart rate was determinable, progressive tachycardia accompanied the development of pulmonary hypertension and tachypnea.

#### DISCUSSION

*A. Circulatory Changes Following Pulmonary Embolism.*—These investigations indicate that the initial and primary effect of major and multiple minor pulmonary embolisms is an abrupt rise in systolic and diastolic pulmonary pressures. On the basis of the pea seed and starch granule embolism it would seem that up to a certain limit indicating complete obstruction the magnitude of pulmonary pressure elevation varies directly with the degree and extent of the mechanical obstruction to blood flow through the lesser circuit. It has been shown that following massive pulmonary embolism there is a fall in the minute volume output of the heart.<sup>1</sup> Although no measurements of cardiac output were performed in these experiments, using the systemic arterial blood pressure as one index of cardiac minute output, our results with starch embolism would offer suggestive evidence that similar hemodynamic changes follow multiple minor embolism. Such decreases in cardiac minute output appear to depend upon the degree of mechanical obstruction in the pulmonary bed. However, the relative stability of the systemic arterial pressure despite the presumptive decrease in cardiac output would indicate that the buffer nerve mechanisms caused peripheral vasoconstriction to maintain the blood pressure level.

The changes in venous pressure were variable. Sometimes it remained unchanged, more frequently it rose, occasionally it fell. Aside from the remote possibility of active local neurogenic venous vasoconstriction or dilatation, the systemic venous bed functions in a passive manner, venous pressure changes being dependent upon the relationship of cardiac out-

dyspnea and tachypnea with an apparent increase in amplitude. Terminally, however, when the pulmonary and systemic arterial pressures began to fall rapidly, respiration slowed markedly and became stertorons. Increasingly severe cyanosis which became intense terminally was observed in all animals.

Changes in heart rate were inconstant. In 2 dogs progressive tachycardia developed, with the apparent advent of ventricular fibrillation terminally in 1 dog. In the remaining dogs variations in the cardiac rate were minimal until terminally when a marked bradycardia appeared with rates of 54 and 12 per minute. The exact nature of this bradycardia whether of sinus origin, or due to the development of complete or to partial A-V block, or to some other mechanism, was undetermined.

**B. MULTIPLE EMBOLISM OF PULMONARY ARTERIOLES AND CAPILLARIES.**—A 1:20 suspension of starch granules in distilled water was used in all 4 animals studied. Two dogs received a total dose of 50 c.c. of the suspension in one injection while the remaining 2 dogs received total amounts of 75 and 200 c.c. of the suspension, in divided doses.

At necropsy, the findings were essentially alike. The right heart appeared markedly dilated. The lungs were pale pink with no apparent gross edema fluid. Microscopically, however, small focal areas of congestion scattered throughout both lung fields were occasionally observed. In random sections, the granules appeared primarily to have occluded the arterioles, only an occasional granule being found bulging a capillary wall. Embolization was diffuse and extreme, practically all the pulmonary arterioles appearing to have been involved.

The pulmonary arterial pressure showed an abrupt rise in its systolic and diastolic levels. The elevation in pressure could be integrated with the increased pulmonary arteriolar resistance due to the mechanical obstruction by the starch granules in the arterioles, since repeated doses of the suspension produced further increments of pressure elevation. However, it was noted that one dog receiving a single dose of the suspension developed a further rise in pulmonary pressure after the initial elevation, possibly as a result of a gradual dispersion of the granules to previously nonoccluded arterioles or by reflex pulmonary arteriolar vasoconstriction. Terminally in 3 of the 4 dogs, the pulmonary pressure showed a moderate decline.

The systemic arterial pressure changes were not striking. This confirms similar observations by others.<sup>12-14</sup> However, an increase in pulse pressure and a fall in diastolic pressure such as has been reported by Binger and associates<sup>9</sup> was not observed. Noteworthy was the fact that in 1 dog each injection of starch suspension resulted in a slight fall in systemic pressure followed by a rapid return to the control level. Terminally in 1 dog the systemic pressure fell to shock levels. This fall coincided with a similar though less marked decline in pulmonary arterial pressure.

final picture presented in these experiments. Relative coronary insufficiency with consequent myocardial ischemia develops and the heart then begins to fail. Heart failure is progressive, but may be gradual,

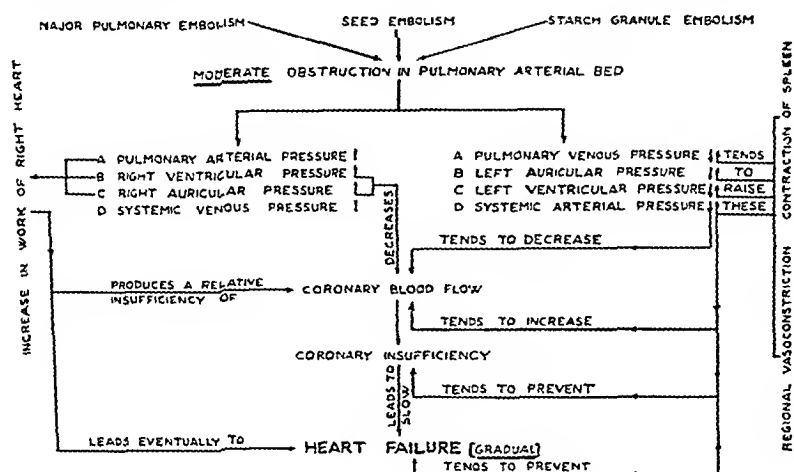


Fig. 1.—Cardiodynamics of pulmonary embolism with gradual failure of the right heart.

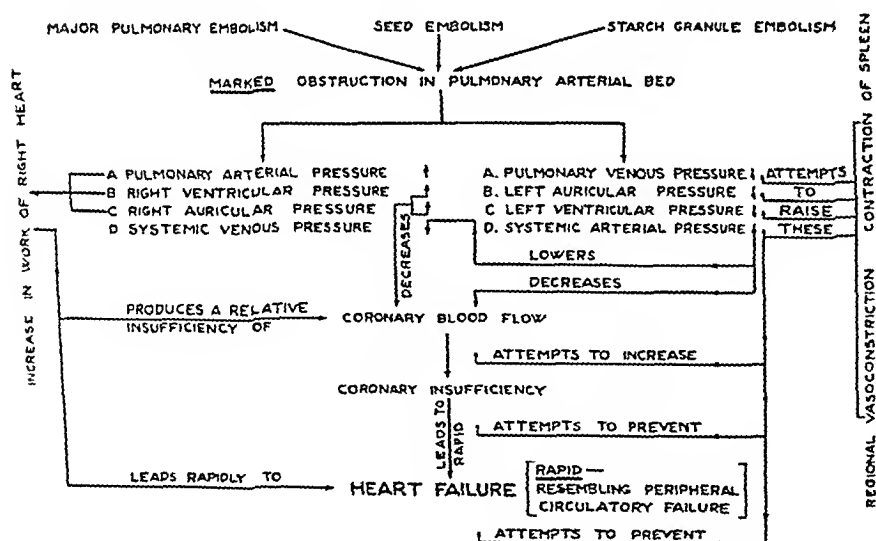


Fig. 2.—Cardiodynamics of pulmonary embolism with rapid failure of the right heart.

in which case death apparently results from extreme right heart failure (Fig. 1); or it may be rapid, in which case death presents itself as the picture of what has been termed hypokinetic circulatory failure (Fig. 2). The mechanism is, however, still the same and represents the syndrome of a right heart that cannot meet its load. This viewpoint coincides with experimental observations on the mechanism of heart failure made in this laboratory.<sup>15</sup>



put to the venous return and subject to changes in the amount of blood in circulation. The effect of obstruction secondary to pulmonary embolism upon venous pressure is twofold and antagonistic. By obstructing the flow of blood through the pulmonary bed it tends to cause accumulation of blood in the right heart and systemic veins and so tends to raise the venous pressure, while by decreasing the minute volume output of the heart it reduces the venous return and so tends to lower the venous pressure. The net effect of these two actions will then determine the level of the venous pressure at any instant (except so far as changes in the amount of blood in circulation come into play). Thus when the fall in cardiac minute output is disproportionally greater than the stasis behind the pulmonary obstruction as indicated by the elevation of pulmonary pressure, the venous pressure will decrease. If on the other hand the reverse be true, the venous pressure will rise. The rise in venous pressure is to be considered as an indication of the mechanism by which the right heart is enabled to attempt to meet the heightened resistance to emptying. By increasing its diastolic volume the right ventricle is enabled to perform a greater amount of work per stroke.

Because of a decrease in cardiac output it has been postulated<sup>1</sup> that the essential cause of death in pulmonary embolism is a specific type of hypokinetic circulatory failure secondary to obstruction in the lesser circuit. In the majority of the experiments we noted that the venous pressure rose following pulmonary embolism. Such elevation associated with a normal systemic arterial and an elevated pulmonary arterial pressure persisted in some animals until death. In other animals, however, in spite of an elevated pulmonary pressure both the systemic arterial and venous pressures tended to fall, reaching shock levels in some instances. Such evidence would superficially indicate that some dogs died apparently as a result of a gradual failure of the right heart indicated by a rising venous pressure while others died as a result of peripheral circulatory collapse indicated by a falling systemic arterial and venous pressure. Careful analysis of the data shows that the two conditions are interrelated and are really variants of the same phenomenon. Essentially one primary mechanism is operating in the death of all these animals. We believe that the primary fault lies in the presence of a foreign object, the embolus in the pulmonary arterial tree. This object acts as a direct mechanical deterrent to the blood flow through the pulmonary circuit. If such an obstruction is not complete, the essential mechanism insuring an adequate flow is accomplished by an increase in the work of the right ventricle. With more complete obstruction the work of the right heart approaches a maximum, and when in spite of this the cardiac output begins to fall, peripheral vasoconstriction follows to aid in maintaining the blood pressure. Further obstruction leads to the

death in pulmonary embolism, particularly since the nerves exert no powerful effects, and, in the dog at least, the vagal fibers are dilators.<sup>25</sup> It was observed that ventricular fibrillation apparently developed in some of the animals and appeared to be the immediate cause of death. It appears more logical, therefore, to believe that such an ectopic rhythm may develop in clinical cases and is the more likely cause for some cases of rapid, "sudden" or unexpected death. This ectopic rhythm, or the premature systoles that lead to it, may be of neurogenic reflex origin, with the efferent path sometimes being over the vagi. In this way rather than by a coronary vasoconstriction can the possibility of "reflex death" be accounted for.

#### SUMMARY AND CONCLUSIONS

1. The mechanism of death and the circulatory changes following major and multiple minor experimentally produced pulmonary embolisms have been investigated in fourteen normal anesthetized or unanesthetized dogs by directly measuring pulmonary and systemic arterial pressures, the systemic venous pressure, heart and respiratory rates. A modification of the London cannula was used to obtain the pulmonary pressure.

2. Major and multiple minor pulmonary embolisms are followed by the development of systolic and diastolic pulmonary hypertension. Systemic arterial pressure changes are not striking. Systemic venous pressure most frequently rises; rarely it falls or shows no change. Heart rate changes are inconstant. Ventricular fibrillation appears terminally in an occasional animal. Rapid respiration develops, usually coincidentally with or soon after the appearance of pulmonary hypertension, and tends to progressively increase. Most frequently progressive cyanosis accompanies the respiratory changes.

3. The theory of reflex coronary vasoconstriction as a cause of "sudden death" finds little support in these experiments, since mechanical factors are enough to explain the possible changes in coronary circulation.

4. The cause of death in pulmonary embolism appears to be due to a rapid or slow failure of the right heart, resulting from the pulmonary vessel obstruction, so-called hypokinetic circulatory failure being in reality *rapid* right heart failure.

We are indebted to Miss L. Friedberg, Mr. M. Feinstein, and Mr. R. Asher for technical assistance in these experiments.

#### REFERENCES

1. Mendlowitz, M.: Experimental Pulmonary Embolism, *J. Thoracic Surg.* 8: 201, 1938.
2. De Takats, G., Beck, W. C., and Fenn, G. K.: Pulmonary Embolism, *SURGERY* 6: 339, 1939.
3. Horn, H., Duck, S., and Friedberg, C. K.: Cardiac Sequelae of Embolism of the Pulmonary Artery, *Arch. Int. Med.* 64: 296, 1939.

B. *Mechanism of Death in Experimental Pulmonary Embolism.*—In these and in a series of experiments that will form the basis of subsequent reports dealing with the effects of various therapeutic agents on and the mechanism of dyspnea and tachypnea in experimental pulmonary embolism, we have observed no instance of so-called "sudden death." Pilcher<sup>16</sup> has stated that one need not invoke reflex mechanisms to explain sudden fatalities in pulmonary embolism, sufficient anatomic changes being always present to account for the death in such cases. Various investigators,<sup>17, 18, 19</sup> however, have postulated sudden vagal stimulation with reflex coronary vasoconstriction to explain cases such as these and present electrocardiographic evidence to support these contentions. As further proof they indicate that the electrocardiographic patterns are improved by abolishing vagal activity either surgically or pharmacologically. Before this view is accepted, it is necessary to consider the factors which influence coronary flow relative to the needs of the heart. As the work from this laboratory<sup>20-24</sup> has shown, total coronary flow depends upon a number of factors among which are: (1) the pressure in the aorta which determines the coronary driving force, the flow varying directly with the pressure; (2) the extent of extravascular compression, the flow varying inversely with the degree of compression which is determined by the distention of the heart; (3) the presence of local tissue metabolites in the myocardium which accumulate in anoxemia and ischemia and tend to dilate the coronary arteries and so increase the coronary flow; and (4) the degree of Thebesian vein and coronary sinus flow which varies inversely with the height of the pressure in the right ventricle and auricle, respectively.

Following pulmonary embolism we have demonstrated an increase in pulmonary pressure and presumably therefore in right ventricular pressure. This by increasing extravascular compression and by affecting the Thebesian veins will tend to diminish coronary flow. The elevation in right auricular pressure as shown by elevation in venous pressure also operates to decrease coronary flow by slowing the emptying of the coronary sinus and veins draining into it. When to this is added the fact that the work of the right ventricle increases as a result of the embolus, as shown by the rise in pulmonary pressure, one need postulate no theoretical coronary vasoconstriction to account for the electrocardiographic changes, for such changes can be readily explained on the basis of relative coronary insufficiency brought on by the net effect of the aforementioned factors. No change in driving force occurs to compensate for these factors since no striking change in systemic arterial pressure occurs to increase coronary flow. In fact, terminally the drop in systemic arterial pressure would be a further factor in slowing the coronary flow at that time. There is no reason to believe that metabolites of a dilator nature compensate for this decrease in relative coronary flow. In view of these facts, there is little to support the reflex theories of

## REDUCTION OF SUPRACONDYLAR FRACTURE IN CHILDREN

VERNON L. HART, M.D., MINNEAPOLIS, MINN.

**S**UPRACONDYLAR fracture of the elbow with displacement of bone fragments and marked generalized swelling about the elbow presents a very difficult problem for the physician and a serious one to the child. Immediate manipulative reduction in acute flexion is the ideal treatment of the fresh fracture before swelling develops. Manipulative reduction in acute flexion, however, is not the ideal method of treatment of the fresh fracture associated with marked swelling and blebs. I have treated this group of children during the past ten years by a method which has proved so efficient that I now wish to present it to the profession.

A Kirschner wire is drilled transversely through the proximal end of the shaft of the ulna (not through the olecranon process) to obtain four or six pounds of skeletal traction (Figs. 3 and 4). Either local or general anesthesia may be used. The line of skeletal traction is directed upward and forward in relation to the elbow since the distal fragment of the fractured humerus is posterior and proximal (Fig. 1). Countertraction is obtained through the patient's body weight and by attaching a weight of about one to three pounds to a padded linen towel which is placed over the abducted arm (Figs. 3 and 4). The entire arm extends beyond the edge of the bed. The bed may be elevated several inches on the side of the injured arm or sand bags may be placed between the mattress and springs above and below the arm to protect the child from the danger of falling out of bed.

Ulnar or radial displacement of the distal fragment of the humerus can be corrected by digital pressure and counter pressure (Fig. 2). The hand is supported with the help of a hand grip while the forearm is supported by a circular piece of felt which is pinned to the traction apparatus (Figs. 3 and 4).

Reduction of the fracture is a gradual process. Good reduction can always be accomplished if treatment is started while the fracture is fresh or before the formation of callus. I have seen considerable callus formation in supracondylar fractures of children ten days after the injury. Anterior and lateral portable radiograms are obtained and studied as frequently as necessary.

Active exercises of the fingers, thumb, and wrist as well as pronation and supination of the forearm are encouraged at the very beginning. Active elbow exercises are started as soon as radiograms reveal callus formation. The skeletal traction treatment is continued until radiograms

4. London, E. S., and Chlaponina, S. J.: Thorakale Angiostomie; Stomosierung der Gefäße eines Lungenlappens (des arteriellen Zweiges), *Ztschr. f. d. ges. exper. Med.* 102: 127, 1937.
5. Daly, I. deB.: The Pulmonary Arterial Pressure in the Unanesthetized Dog, *J. Physiol.* 91: 14, 1937.
6. Hamilton, W. F., Woodbury, R. A., and Vogt, E.: Differential Pressures in the Lesser Circulation of the Unanesthetized Dog, *Am. J. Physiol.* 125: 130, 1939.
7. Katz, L. N., and Steinitz, F. S.: Pulmonary Arterial Pressure in Experimental Renal Hypertension, *Am. J. Physiol.* 128: 433, 1940.
8. Binger, C. A. L., Brow, G. R., and Branch, A.: Experimental Studies on Rapid Breathing; Tachypnea, Dependent Upon Anoxemia, Resulting From Multiple Emboli in the Larger Branches of the Pulmonary Artery, *J. Clin. Investigation* 1: 155, 1924.
9. Binger, C. A. L., Brow, G. R., and Branch, A.: Experimental Studies on Rapid Breathing; Tachypnea, Independent of Anoxemia, Resulting From Multiple Emboli in the Pulmonary Arterioles and Capillaries, *J. Clin. Investigation* 1: 127, 1924.
10. Hamilton, W. F., Brewer, G., and Brotman, T.: Pressure Pulse Contours in the Intact Animal, *Am. J. Physiol.* 107: 427, 1934.
11. Katz, L. N., Friedman, M., Rodbard, S., and Weinstein, W.: Observations on the Genesis of Renal Hypertension, *Am. Heart J.* 17: 334, 1939.
12. Dunn, J. S.: The Effects of Multiple Embolism of Pulmonary Arterioles, *Quart. J. Med.* 13: 129, 1920.
13. Weleh, W. H.: Zur Pathologie des Lungenödems, *Virchow's Arch. f. path. Anat.* 72: 375, 1878.
14. Underhill, S. W. F.: An Investigation Into the Circulation Through the Lungs, *Brit. M. J.* 2: 779, 1921.
15. Katz, L. N.: Observations on Cardiac Failure and the Mode of Its Production, *Am. A. Advance Sc.* 13: 184, 1940.
16. Pilcher, R.: The Role of Obstruction in Fatal Embolism, *Lancet* 1: 1257, 1939.
17. Mosler, E.: Ueber Kreislaufvorgänge bei der Lungenembolie, *Med. klin.* 27: 1555, 1931.
18. Radnai, P., and Mosonyi, L.: Ueber den gefäßverengernden Pulmonocoronar reflex, *Ztschr. f. d. ges. exper. Med.* 98: 651, 1936.
19. Scherf, D., and Schönbrunner, E.: Ueber den pulmoeoronaren Reflex bei Lungenembolien, *Klin. Wehnsehr.* 16: 340, 1937.
20. Katz, L. N., Jochim, K., and Bohning, A.: The Effect of the Extravascular Support of the Ventriles on the Flow in the Coronary Vessels, *Am. J. Physiol.* 122: 236, 1938.
21. Katz, L. N., Jochim, K., and Weinstein, W.: The Distribution of the Coronary Blood Flow, *Am. J. Physiol.* 122: 252, 1938.
22. Katz, L. N., and Lindner, E.: Quantitative Relation Between Reactive Hyperemia and the Myocardial Ischemia Which It Follows, *Am. J. Physiol.* 126: 283, 1939.
23. Katz, L. N., and Lindner, E.: The Reaction of the Coronary Vessels to Drugs and Other Substances, *J. A. M. A.* 113: 2116, 1939.
24. Jochim, K.: Vascular and Extravascular Factors Influencing Coronary Blood Flow, *Am. A. Advance Sc.* 13: 94, 1940.
25. Katz, L. N., and Jochim, K.: Observations on the Innervation of the Coronary Vessels of the Dog, *Am. J. Physiol.* 126: 395, 1939.

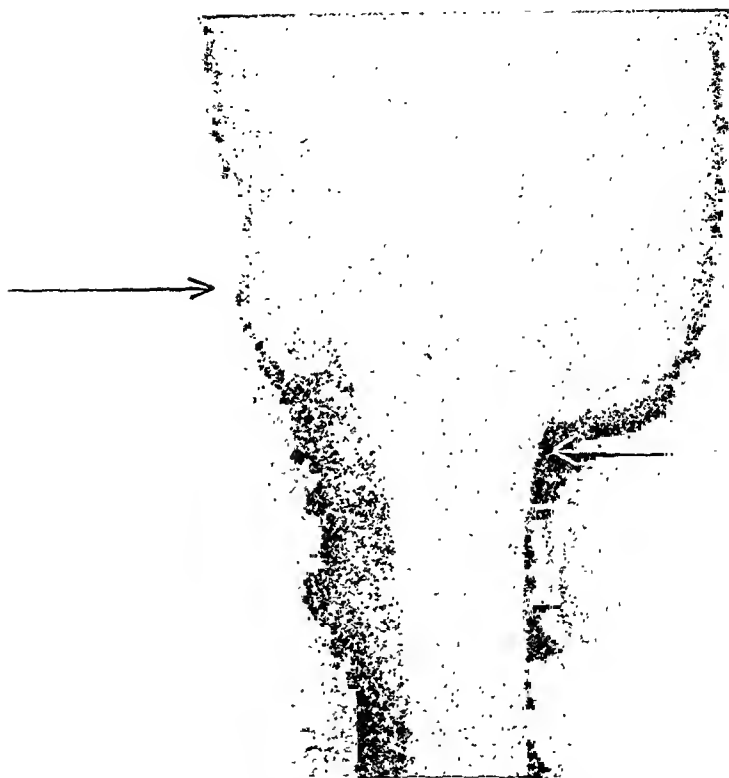


Fig. 2.—Anteroposterior radiogram of supracondylar fracture of elbow showing ulnar displacement of the distal fragment of the humerus. This displacement is readily corrected by digital pressure. The reduction is maintained by continuous horizontal traction attached to the ulnar end of the Kirschner wire. With radial displacement of the distal fragment the traction would be attached to the radial end of the Kirschner wire.



Fig. 1.—Lateral radiogram of supracondylar fracture with the usual posterior and proximal displacement of the distal fragment, elbow, and forearm. The arrows indicate the line of skeletal traction and towel countertraction on the ulna and arm respectively. The fracture is gradually reduced by the traction forces. Immediate manipulative reduction in acute flexion is contraindicated because of marked hemorrhage and soft tissue swelling about the elbow. Reduction by open operation is not necessary.

This method of gradual reduction of supracondylar fracture in children is advised when immediate manipulative reduction fails or when manipulative reduction is contraindicated because of extensive hemor-



Fig. 1.—See opposite page for legend.

rhage and marked generalized swelling of the elbow. The method is ideal because it is mechanically efficient, the patient is comfortable, the extremity is elevated, and the entire extremity is exposed for vigilant inspection of the integrity of the circulatory and neuromuscular systems.





of the study. Hypoproteinemia was induced by a low-protein diet and repeated plasmapheresis. This method not only reduces the plasma protein concentration but depletes the labile protein reserve of the body as a whole. The diet was designed to be adequate for all of the animal's requirements except protein. It was made up as follows: carrots, 4.5 kg.; turnips, 4.5 kg.; rice, 2.0 kg.; oleomargarine, 1.6 kg.; cod-liver oil, 100 c.c.; bone ash, 50 Gm.; sodium chloride, 100 Gm.; yeast concentrate, 5 Gm.

A.



B.

Fig. 2.—A. Roentgenogram of left foreleg of Dog 699 forty-five days after fracture of the ulna. The animal was hypoproteinemic during this period as shown in Fig. 1. B. Roentgenogram of right foreleg of Dog 699 thirty-nine days after fracture of the ulna. The plasma protein concentration had been restored to normal. There is a greater amount of callus visible by x-ray.

The carrots and turnips were coarsely ground and boiled for twenty minutes with the rice. The other ingredients were then added with the exception of the cod-liver oil and yeast, which were not added until the mixture had cooled. The stock food was carefully mixed and refrigerated. The protein content of the diet was approximately 1 per cent. The dogs were given as much as they desired every day.

Plasmapheresis was carried out by aspirating blood from the femoral artery into sterile 250 c.c. centrifuge bottles containing sufficient sodium citrate to prevent coagulation. After centrifugation the plasma was aspirated from the bottles and the cells diluted with normal saline solution and returned, usually within an hour, to the animal from which it had been taken. The bleeding was carried to the point of mild air hunger. It was usually possible to remove 350 to 400 c.c. of blood at

# THE INFLUENCE OF HYPOPROTEINEMIA ON THE FORMATION OF CALLUS IN EXPERIMENTAL FRACTURE

JONATHAN E. RHOADS, M.D., AND WILLIAM KASINSKAS, B.A.,  
PHILADELPHIA, PA.

(From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania)

**H**YPOPROTEINEMIA has been shown to retard healing in soft tissue wounds in dogs,<sup>1, 2</sup> and it has recently been shown that hypoproteinemia is frequently present in patients with wound disruption.<sup>3</sup> These observations and the well-known relationship between the serum calcium and the serum proteins suggested that hypoproteinemia might also exert an adverse influence on the healing of fractures. In 1937 Kernwein<sup>4</sup>

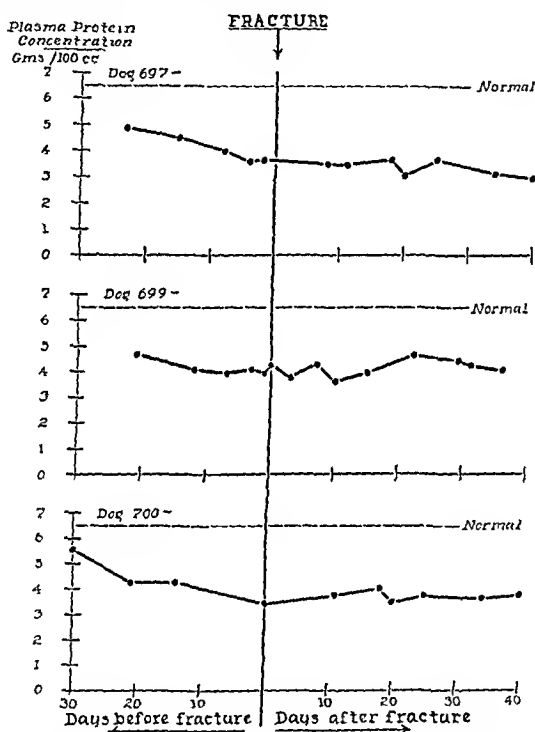


Fig. 1.—Plasma protein levels of hypoproteinemic dogs from before time of fracture until hypoproteinemic regimen was completed.

found that fracture healing in rabbits was retarded by starvation. A protein deficiency very probably developed in these animals, but as there also would have been a deficiency of other factors, the experiments are difficult to interpret. The following study was undertaken to determine as directly as possible the effect of hypoproteinemia on the formation of bony callus following fractures in dogs.

## METHOD

Medium-sized mongrel dogs were employed. These animals came from agricultural communities and appeared entirely normal at the beginning

Three dogs were rendered hypoproteinemic in the late spring of 1938 and the left ulna of each animal was sectioned about two inches above the distal end. All the wounds healed per primam. The plasma protein concentrations of these animals are shown in Fig. 1. After a period of six weeks the hypoproteinemic regime was ended. One of the animals died during the summer but the other two made a complete recovery and were used as controls in 1939. At this time their serum protein

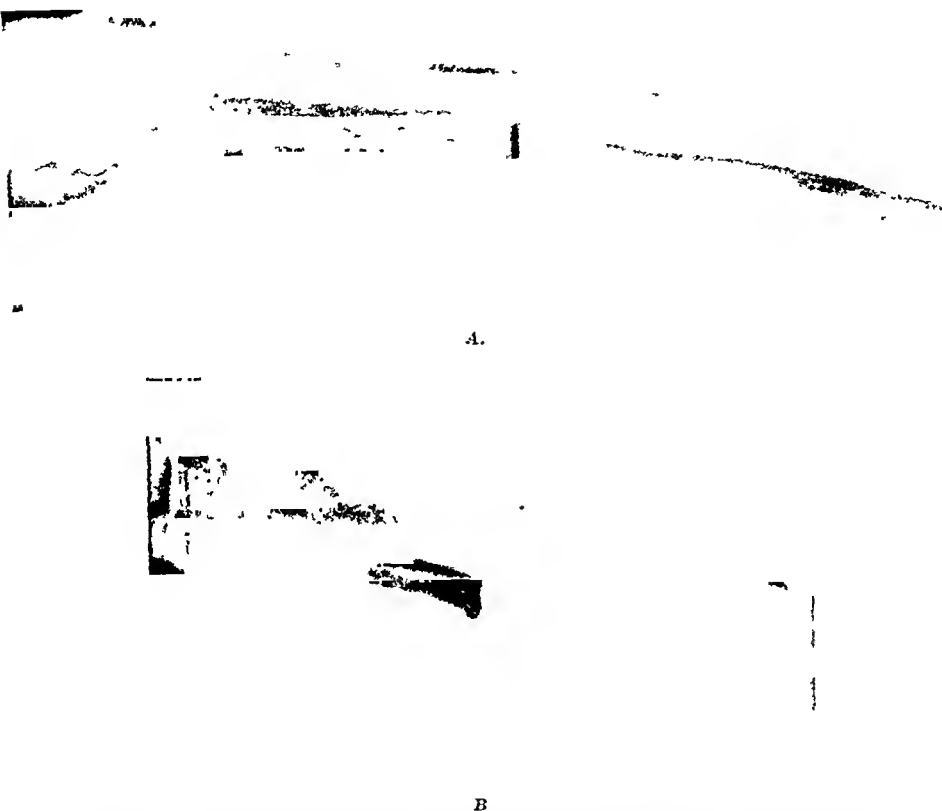
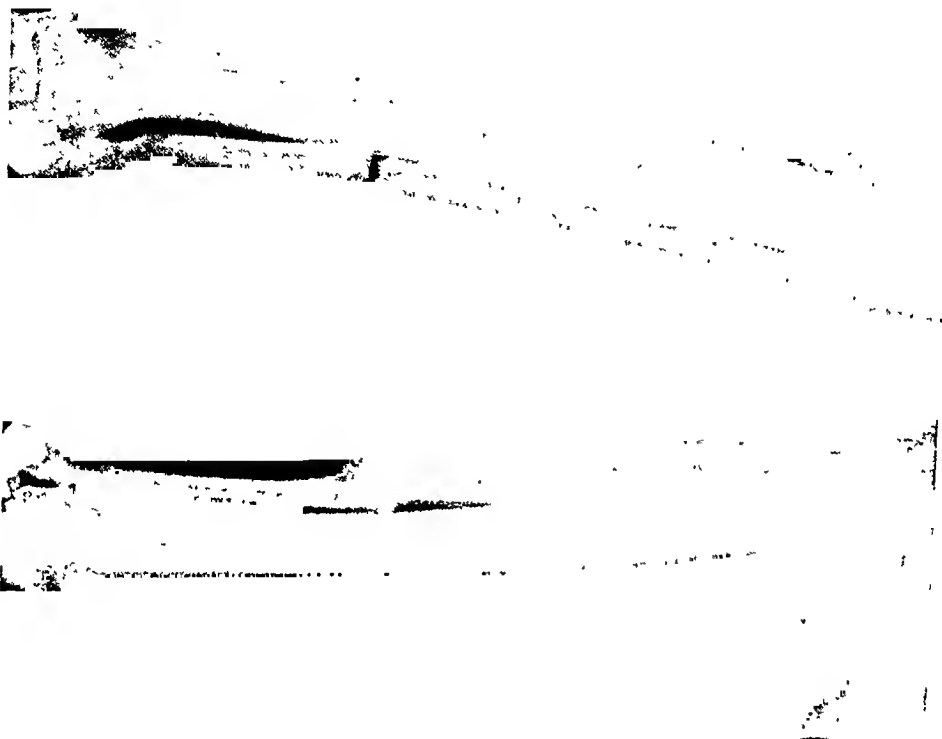


Fig 4—A Roentgenogram of the foreleg of Dog 597 forty days after fracture of the ulna. The animal was hypoproteinemic during this period as shown in Fig 1. B Roentgenogram of the foreleg of Dog 904 forty days after fracture of the ulna. The plasma protein concentration was normal

levels were within the normal range and Gigli saw section of the right ulna was carried out at approximately the same level. Later another normal dog was used for the third control. The x-ray evidence of callus formation at forty to forty-five days in the hypoproteinemic dog is compared with that seen after about the same interval in the normal dog (Figs 2, 3, and 4). A later comparison showing the callus formation in the hypoproteinemic dogs at sixty to seventy-four days as compared with that in the control fractures at about sixty days is shown in Figs. 5, 6, and 7.

a time, and the procedure was carried out about three times per week until the serum protein level declined to below 4 Gm. per cent. Following this plasmapheresis was repeated often enough to maintain the protein concentration at about this level for a period of six weeks following fracture.

A.



B.

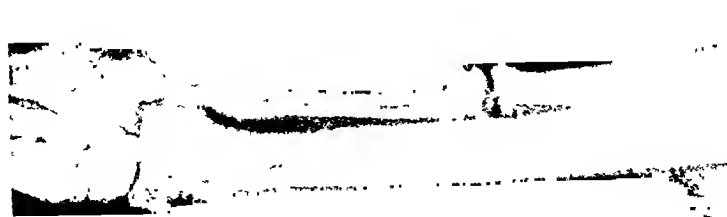
Fig. 3.—A. Roentgenogram of left foreleg of Dog 700, forty days after fracture of the ulna. The animal was hypoproteinemic during this period as shown in Fig. 1. B. Roentgenogram of right foreleg of Dog 700 thirty-nine days after fracture of the ulna. The plasma protein concentration had been restored to normal and more callus is seen.

During the control periods the diet consisted of table scraps. Stock dogs subsisting on this diet maintain plasma protein concentrations of 6 to 7 Gm. per cent.

The type of fracture chosen for the study was Gigli saw section of the ulna. The advantages of this fracture for experimental work lie in the fact that the radius acts as a splint and that the position of the fragments, the direction of the line of fracture, and the degree of fixation all are relatively constant. The fracture is also readily accessible for x-ray examination. Furthermore, union occurs very slowly, probably on account of the separation of the fragments, so that callus formation can be studied over a considerable period. The separation of the fragments makes it somewhat easier than usual to study the development of bony callus roentgenographically.

The circulation of the hypoproteinemic animal may be considerably altered. Whipple and his associates have noted a marked decrease in plasma volume in their plasma-depleted animals. It is well known that a large fraction of the serum calcium is bound to the serum protein so that when serum protein concentration is low, serum calcium concentration is also reduced. It is not possible at the present time to state by what mechanism the hypoproteinemic state interfered with the formation of bony callus. It is important always to keep in mind that hypoproteinemia is not an abnormality that exists alone but one which is associated with many physiologic alterations.

A.



B.

Fig. 6.—A. Roentgenogram of left foreleg of Dog 700 sixty-four days after fracture showing some callus formation. The protein depleting regime had been stopped, but callus formation is still retarded as compared with that seen in Fig. 6B. B. Roentgenogram of right foreleg of Dog 700 sixty-three days after fracture. The plasma protein concentration was normal throughout this experiment.

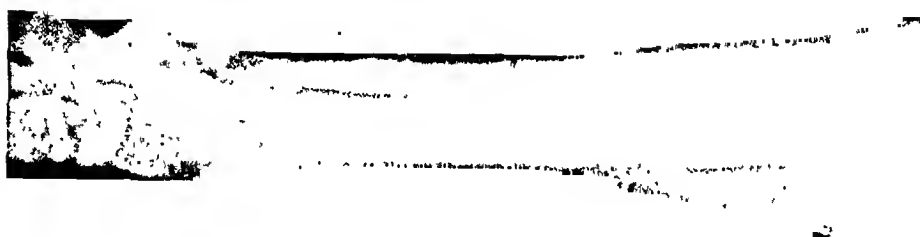
The differences noted in these animals were consistent not only in the roentgenograms shown but in others taken at intervening periods. The use of two of the three hypoproteinemic animals as their own controls tends to eliminate the influence of unknown constitutional and individual factors. It should be noted that these two animals were almost a year younger at the time of the hypoproteinemic phase than at the time of the control fracture so that in so far as age is a factor it should have diminished the effect observed.

Hypoproteinemia has not been observed clinically by us as a cause of delayed union. Other factors induce such wide variations in the rate of

The fact that callus proliferation was so much more abundant in Dog 700 than in Dog 699 is probably due to a difference in age which was not realized at the beginning of the experiment. Dog 699 appeared to be rather an old animal; whereas, Dog 700 had not attained its full growth when the experiment began. Both of the other dogs appeared to be mature but not old. However, their actual ages were not known.

In all six comparisons it will be seen that less callus formation occurred when the animals were hypoproteinemic.

A.



B.

Fig. 5.—A. Roentgenogram of the left foreleg of Dog 699 seventy-four days after the fracture. Although the protein depleting regime had been stopped, callus is still not visible. B. Roentgenogram of the right foreleg of Dog 699 sixty-three days after fracture. A faint zone of callus is visible which almost bridges the gap between the ends of the ulna.

#### DISCUSSION

Many factors have been studied in connection with fracture healing. Some of these appear quite basic such as calcium metabolism, and the influence of vitamin D, while others are more obscure, such as vitamin E and orchidectomy. Vitamin C has also been studied in this connection, but the role of the plasma proteins has not received much attention in recent years.

Proteins are seldom thought of in connection with bones yet like all living tissues the bones undoubtedly require protein for growth. Furthermore, the first phase of fracture healing appears to consist in the formation of granulation tissue between the fragments. Here fibroplasia plays a role and severe hypoproteinemia has been shown to retard this process seriously.

## SECONDARY OR POSTOPERATIVE PAROTITIS

GORDON F. MADDING, M.D.,\* AND ROBERT E. FRICKE, M.D.,  
ROCHESTER, MINN.

*(From the Mayo Foundation and the Section on Radium Therapy, the Mayo Clinic)*

ALTHOUGH parotitis is a rare postoperative complication, it does occur with sufficient frequency to justify the interest of every physician. Numerous theories have been advanced concerning the etiology factors in this condition, chief of which are (1) degeneration of the parotid gland as a result of high fever, (2) degeneration of the parotid gland attributable to surgical procedures on the generative system, (3) the toxin theory, (4) involvement of the gland by infected emboli from the operative site, (5) infection extending through the lymphatics from an adjacent inflammatory process, and (6) ascending infection of the parotid gland by way of Stensen's duct.

It is the consensus today that the theory of ascending infection is the one most tenable. Berndt, Buck, and Buxton<sup>1</sup> carried out some interesting experimental work, in which they demonstrated the ease with which the parotid gland may become infected through the duct as compared with the hematogenous route. Seifert<sup>2</sup> also called attention to the infrequent appearance of suppurative parotitis in cases of staphylococic septicemia.

The clinical picture of secondary parotitis usually is clear-cut and the diagnosis is made easily. Onset occurs most often between the first and fifth postoperative days, but it may occur at any time. It is associated with fever, swelling over the parotid gland, and in all cases some degree of discomfort which is most marked on opening and closing of the jaw. On examination, the orifice of Stensen's duct usually is visibly inflamed. Besides the redness and swelling about the orifice, turbid saliva or pus may be expressed by gently massaging along the course of the duct. This is not necessary to make the diagnosis and is a practice which probably should be condemned because of the added discomfort to the patient. Rarely is the seventh cranial nerve involved and then only when suppuration is present.

There seems to be an almost universal misunderstanding as to the severity of this condition. In fatal cases the course often is rapid, but almost without exception this is due to other pathologic processes within the body. If death occurs, parotitis usually is not more than a contributory cause and in many cases has disappeared completely before death. The generally held belief that parotitis is a local process produced by an ascending infection through Stensen's duct makes it hardly understandable that it could have the high mortality rate so frequently attributed to it. Green<sup>3</sup> found that mortality rates in individual reports in the literature ranged from 25 to 60 per cent. Pearson<sup>4</sup> quoted the

Received for publication, April 2, 1941.

\*Fellow in Surgery, the Mayo Foundation.



fracture repair in patients that it seems doubtful whether opportunity for an adequate evaluation of the role of hypoproteinemia in fracture healing in patients will be available to any one clinic unless in certain parts of the world food shortage should cause an epidemic of hypoproteinemia.



A.

B.

Fig 7—A. Roentgenogram of foreleg of Dog 697 sixty days after fracture. Hypoproteinemia had been maintained until shortly before this examination was made. B. Roentgenogram of foreleg of Dog 901 sixty-one days after fracture. The plasma protein concentration was normal.

#### CONCLUSION

Experimental data are presented indicating that severe hypoproteinemia retards the formation of bony callus in fractures produced in dogs by section of the ulna with a Gigli saw.

#### REFERENCES

1. Thompson, W. D., Raydin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption, *Arch. Surg.* 36: 509, 1938.
2. Thompson, W. D., Raydin, I. S., Rhoads, J. E., and Frank, I. L.: Use of Lyophilized Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption, *Arch. Surg.* 36: 509, 1938.
3. Hartzell, J., Winfield, J. M., and Irwin, J. L.: Plasma Vitamin C and Serum Protein Levels in Wound Disruption, *J. A. M. A.* 116: 669, 1941.
4. Kernwein, G.: Effect of Starvation on Healing of Fractures in Rabbits, *Arch. Surg.* 35: 492, 1937.

used in the intervening periods. It is best perhaps to use cold packs first; if there is evidence of suppuration, heat in the form of poultices is probably more efficacious in localizing the process. Leithauser and Cantor<sup>9</sup> recommended the use of massive doses of compound solution of iodine (Lugol's solution). Intravenous administration of mercurochrome was used previously, but of late this method has been largely abandoned because of failure of support of the early belief that mercurochrome had a specific effect on staphylococci.

The use of radium was recommended early by Rankin and Palmer and later by Bowling and one of us (R. E. F.). Of the two methods of radiation therapy, namely radium and roentgen rays, the latter is probably the method of choice as the length of treatment is shortened and the discomfort to the patient with the use of radium packs is obviated. It should be borne in mind that suppuration may not be evidenced by fluctuation because of the firm capsule which encases the gland. It is well, however, to wait until fluctuation is present before resorting to incision. If pus is suspected, aspiration may be of help in determining its presence. Numerous incisions have been recommended, but the Y-shaped incision as suggested by Fisher<sup>10</sup> is perhaps as satisfactory as any.

#### CONCLUSIONS

From study of our series of cases of postoperative parotitis, the following conclusions seem warranted.

1. Acute, secondary parotitis is a postoperative complication which is rarely seen.
2. The mortality rate associated with this condition is low, but if suppuration occurs, morbidity may be great.
3. The route of infection usually is by way of Stensen's duct.
4. Prophylactic treatment should be directed to the mouth.
5. Radiation therapy reduces the morbidity of this complication.
6. Surgical drainage rarely is indicated and then only in the presence of suppuration.

#### REFERENCES

1. Berndt, A. L., Buck, R., and Buxton, R. von L.: Pathogenesis of Acute Suppurative Parotitis. Experimental Study, *Am. J. M. Sc.* 182: 639-649, 1931.
2. Seifert, E.: Ueber den Infektionsweg bei postoperativer Parotitis, *Deutsche Ztschr. f. Chir.* 198: 387-400, 1926.
3. Green, M. T.: Post-operative Parotitis as a Complication of Abdominal Surgery, *Tri-State M. J.* 7: 1406-1408, 1935.
4. Pearson, E. A.: Parotitis and Staphylococcus Aureus Septicemia as Surgical Complications, *West. J. Surg.* 47: 468-473, 1939.
5. Blair, V. P., and Padgett, E. C.: Pyogenic Infection of the Parotid Glands and Ducts, *Arch. Surg.* 7: 1-36, 1923.
6. Rankin, F. W., and Palmer, B. M.: Post-operative Parotiditis; Treatment With-out and With Radium, *Ann. Surg.* 92: 1007-1013, 1930.
7. Bowling, H. H., and Fricke, R. E.: Radium Treatment of Post-operative Parotitis, *Radiology* 26: 37-40, 1936.
8. Talbot, H. S.: Acute Suppurative Parotitis; Its Etiology, Pathogenesis and Treatment, *Am. J. Surg.* 25: 267-276, 1934.
9. Leithauser, D. J., and Cantor, M. O.: Massive Doses of Lugol's Solution in Acute Secondary Parotitis, *Ann. Surg.* 111: 650-654, 1940.
10. Fisher, W. H.: Post-operative Infective Parotiditis, *Ann. Surg.* 78: 568-571, 1923.

combined American statistics as indicating a mortality rate of 58 per cent, with an incidence of the disease of 1 case in 2,275 cases in which operations were performed. Blair and Padgett<sup>5</sup> gave a mortality rate of 50 per cent in their cases. Raukin and Palmer<sup>6</sup> in a review of 79 cases collected from the literature found a mortality rate of 46 per cent; Bowing and one of us (R. E. F.)<sup>7</sup> found a mortality of 6 per cent. Talbot<sup>8</sup> was one of the first to call attention to the overemphasis which has been placed on the excessive mortality rates attributed to postoperative parotitis.

Our study consisted of 190 cases of postoperative parotitis; in 81 conservative measures were employed and in 109 cases radiation therapy. In this series 1 death could be attributed directly to the parotitis, a mortality rate of less than 1 per cent. The condition was associated most frequently with operations which involved the colon, pelvis, biliary tract, and stomach in that order.

We wish to stress the low mortality rate associated with this condition, although active treatment is indicated when the complication is first noted. In 7 of 18 cases in our series in which death occurred there was some evidence of parotitis at the time of death. In all but 1 of these 7 cases the coexisting pathologic processes were of such a nature that it is hard to conceive that parotitis played more than a contributory part as a cause of death. Because of the low mortality rate associated with parotitis we have omitted intentionally any comparison of figures on the number of deaths of patients treated with radium as compared to those treated by conservative measures.

If parotitis does not have a high mortality rate, then morbidity is the next most important consideration. When surgical drainage of the parotid gland becomes necessary, it adds to the necessary period of hospitalization and to the expense of the patient. From this standpoint radiation therapy seems to have a definite place in the treatment of this complication, for suppuration occurred twice as often in the group treated by conservative measures.

If the hypothesis that ascending infection by way of Stensen's duct is most often responsible for postoperative parotitis is accepted, then it seems rational that all prophylactic treatment should be directed to the mouth. This should include the avoidance of dehydration of the patient and careful hygiene of the mouth. Every effort should be made to stimulate the secretion of saliva by the use of chewing gum, slices of lemon and orange, or candy, and the avoidance of the use of those drugs which would tend to diminish the free flow of saliva.

Parotitis usually is treated by the conservative method or by irradiation. Operative intervention at present is reserved for those cases in which suppuration occurs. Conservative treatment consists of the application of warm packs or ice packs and the use of diathermy by the air-spaced method. Diathermy by this method consists of placing the unit 1 to 2 cm. from the involved parotid gland, thus avoiding contact with the involved tissue. One to two treatments are given daily for thirty minutes each. In addition to diathermy, hot or cold packs are

be a pure strain, selected for high cancer incidence. The mice were individually caged in galvanized iron cages, partly wire mesh and partly sheet. They were fed once a day in nonspill cups made from ointment tins, the covers of which were cut to admit the head of a mouse. The proper amounts of the restricted diet, fed at different ages, were measured by putting the food into hollowed-out brass molds, cut to hold the desired quantity by weight. The diet was put into the mold, scraped off evenly, then tapped out into the food cup. A wire mesh disk inserted above the food prevented spillage from both the restricted and *ad libitum* feeders. Tap water was continuously available. The animals were housed from the age of 1 month in a room with the temperature controlled at  $80^{\circ} \pm 2^{\circ}$  F., and the relative humidity at  $45 \pm 15$  per cent saturation. The animals were identified by ear tattoo. Weights were recorded weekly at which time careful inspection and palpation were made for discovery of tumors. Tumorous animals were sometimes allowed to die spontaneously but were usually sacrificed under ether after the masses had become large. A complete examination was made of the entire mammary region in animals dying of whatever cause. The lungs and liver were also examined carefully, but other organs have not been studied consistently. Any tissue presenting an abnormal appearance at autopsy was preserved, and portions were sectioned, stained, and studied microscopically.

The control mice were fed the diet indicated below in unrestricted amount. Food was kept before the animals at all times and the amount ingested measured by weighing. The restricted mice were fed an amount of protein, vitamins, and minerals approximately equal to that actually ingested by mice eating the control diet *ad libitum*, but the amounts of carbohydrates and fat fed were reduced so as to decrease the total caloric intake by about one-third. It should be re-emphasized that each mouse was fed individually a measured amount of food.

TABLE I\*

COMPONENT	CONTROL DIET GM./100	RESTRICTED DIET GM./100
Glucose	33	22.0
Lard	20	15.3
Casein	28	37.4
Dry yeast (Anheuser-Busch Strain G7)	8	10.6
Dry alfalfa leaf	4	5.4
Salt mixture†	7	9.3

\*Each animal was given a supplement of 0.1 cc. of U. S. P. X1 cod-liver oil and the same amount of wheat germ oil each week added directly to the food cup.

†CaCO<sub>3</sub>-543, MgCO<sub>3</sub>-25, MgSO<sub>4</sub>-16, NaCl-69, KCl-112, KH<sub>2</sub>PO<sub>4</sub>-212, FePO<sub>4</sub>-21, KI-0.05.

The composition of the diets employed was as indicated in Table I.

The composition of the restricted diet was calculated on the basis of observations on the food intake of control animals at various ages. The

# THE INFLUENCE OF CALORIC RESTRICTION UPON THE INCIDENCE OF SPONTANEOUS MAMMARY CARCINOMA IN MICE

MAURICE B. VISSCHER, PH.D., M.D., ZELDA B. BALL, B.S.,  
RICHARD H. BARNES, PH.D., AND IVAR SIVERTSEN, M.D.,  
MINNEAPOLIS, MINN.

*(From the Divisions of Physiology and Physiological Chemistry, and the Sivertsen Foundation for Cancer Research of the Medical School of the University of Minnesota\*†).*

## INTRODUCTION

THE possibility that dietary factors play a role in determining susceptibility to cancer has long been recognized. A survey of the literature made in this laboratory revealed about 350 papers bearing upon the problem. This extensive literature cannot be reviewed here. In general it can be said that to our knowledge there is no previous study in which the incidence of spontaneous malignancy has been observed in relation to variations in simple caloric intake, when the ingestion of the known dietary essentials (minerals, vitamins, and amino acids) has been held constant. A number of workers have studied the effects of restriction of total food intake upon cancer incidence. The first suggestive studies of this type in relation to incidence of spontaneous mammary carcinoma in mice are those of Sivertsen and Hastings (1938). Their deduction that reduction in total food intake decreases the incidence was confirmed by Tannenbaum (1940). These observers have presented evidence to show that reduction in amount of all food elements results in a decreased incidence of spontaneous mammary carcinoma in mice.

It appeared to us that no satisfactory solution of the problem of the influence of diet upon cancer incidence was possible unless the effects of alterations of individual factors in the diet were studied separately. We have therefore begun such a detailed analysis with an investigation of the incidence of mammary carcinoma in the  $C_3H$  strain of mice in relation to the caloric content of the diet, holding all other known dietary essentials as nearly constant as possible. Mice of the  $C_3H$  strain were employed because they show a high cancer incidence in the virgin state, and our experience with A strain animals indicated that a caloric restriction greatly reduced fertility.

## METHODS

The  $C_3H$  mice employed in this study were obtained from the Jackson Memorial Laboratories, Bar Harbor, Maine, and were certified to

\*Aided by technical assistance from Sub-Project No. 353-65-171-110, Works Progress Administration, and by funds from the Sivertsen Foundation.

†The advice of Dr. E. T. Bell and Dr. G. O. Parr is gratefully acknowledged.

Received for publication, Dec. 4, 1941.

be a pure strain, selected for high cancer incidence. The mice were individually caged in galvanized iron cages, partly wire mesh and partly sheet. They were fed once a day in nospill cups made from ointment tins, the covers of which were cut to admit the head of a mouse. The proper amounts of the restricted diet, fed at different ages, were measured by putting the food into hollowed-out brass molds, cut to hold the desired quantity by weight. The diet was put into the mold, scraped off evenly, then tapped out into the food cup. A wire mesh disk inserted above the food prevented spillage from both the restricted and *ad libitum* feeders. Tap water was continuously available. The animals were housed from the age of 1 month in a room with the temperature controlled at  $80^{\circ} \pm 2^{\circ} \text{F.}$ , and the relative humidity at  $45 \pm 15$  per cent saturation. The animals were identified by ear tattoo. Weights were recorded weekly at which time careful inspection and palpation were made for discovery of tumors. Tumorous animals were sometimes allowed to die spontaneously but were usually sacrificed under ether after the masses had become large. A complete examination was made of the entire mammary region in animals dying of whatever cause. The lungs and liver were also examined carefully, but other organs have not been studied consistently. Any tissue presenting an abnormal appearance at autopsy was preserved, and portions were sectioned, stained, and studied microscopically.

The control mice were fed the diet indicated below in unrestricted amount. Food was kept before the animals at all times and the amount ingested measured by weighing. The restricted mice were fed an amount of protein, vitamins, and minerals approximately equal to that actually ingested by mice eating the control diet *ad libitum*, but the amounts of carbohydrates and fat fed were reduced so as to decrease the total caloric intake by about one-third. It should be re-emphasized that each mouse was fed individually a measured amount of food.

TABLE I\*

COMPONENT	CONTROL DIET GM./100	RESTRICTED DIET GM./100
Glucose	33	22.0
Lard	20	15.3
Casein	28	37.4
Dry yeast (Anheuser-Busch Strain G7)	8	10.6
Dry alfalfa leaf	4	5.4
Salt mixture†	7	9.3

\*Each animal was given a supplement of 0.1 cc of U. S. P. X1 cod-liver oil and the same amount of wheat germ oil each week added directly to the food cup.

† $\text{CaCO}_3$ -513,  $\text{MgCO}_3$ -25,  $\text{MgSO}_4$ -16,  $\text{NaCl}$ -62,  $\text{KCl}$ -112,  $\text{KH}_2\text{PO}_4$ -212,  $\text{FePO}_4$ -21,  $\text{KI}$ -0.05.

The composition of the diets employed was as indicated in Table I.

The composition of the restricted diet was calculated on the basis of observations on the food intake of control animals at various ages. The

amounts of food eaten by the *ad libitum* controls studied initially and the food allowed the restricted mice at various ages are indicated in Table II.

TABLE II  
FOOD INTAKE

AGE (DAYS)	CONTROLS GM./MOUSE	RESTRICTED MICE GM./MOUSE
30-35	1.6	1.20
36-50	1.8	1.36
51-100	2.0	1.51
101-	2.3	1.74

It will be noted from Table I that 0.75 Gm. of restricted diet contains as much casein, yeast, alfalfa, and salt as 1.0 Gm. of the *ad libitum* diet.

Mice of nearly identical ages were used for the entire study and were divided into the two groups by pairing animals of equal weight at the start of the experiment.

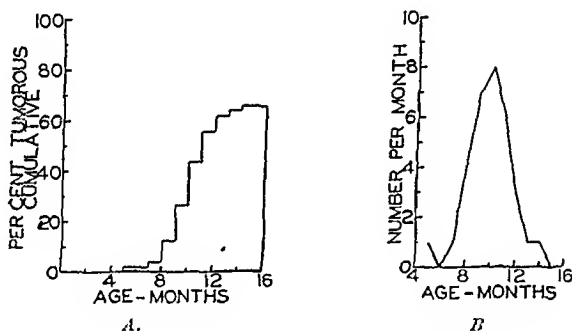


Fig. 1.—A. Spontaneous mammary carcinoma incidence of virgin female C<sub>5</sub>H strain mice on the *ad libitum* diet, cumulative over sixteen months of age. B. Frequency of occurrence in relation to age of cancer incidence in the mice described in A.

## RESULTS

*A. Cancer Incidence and Mortality.*—The times of occurrence of spontaneous mammary tumors proved at autopsy to be carcinoma, and the ages at death of C<sub>5</sub>H virgin female mice on *ad libitum* as compared with calorie restricted diets are presented in Table III. It will be noted that at sixteen months of age no tumors have appeared in the restricted diet mice. At the same age 67 per cent of the animals fed *ad libitum* have developed histologically verified mammary carcinoma. At sixteen months 57 per cent of the restricted mice are still alive while only 29 per cent of the *ad libitum* animals survive. The distribution of cancer incidence with age in *ad libitum* fed mice is seen graphically in Fig. 1, A and B. The cumulative incidence is shown in Fig. 1A and the frequency of occurrence during each age month is shown in Fig. 1B. It

TABLE III  
TUMOR INCIDENCE AND DEATH RATES IN C<sub>3</sub>H STRAIN VIRGIN MICE ON CALORIE RESTRICTED AND AD LIBITUM DIETS

	MONTHS															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
No. restricted living	14	11	11	11	41	44	42	40	39	38	31	34	28	27	27	25
No. restricted dying	0	0	0	0	0	0	2	2	1	1	4	0	6	1	0	2
No. restricted tumors	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
No. ad libitum living	51	51	49	49	48	48	46	42	35	27	21	17	16	15	15	15
No. ad libitum dying	1	0	2	0	1	0	2	1	7	8	6	4	1	1	0	0
No. ad libitum tumors	0	0	0	0	1	0	1	1	7	8	6	3	1	1	0	0
No. ad libitum tumors cumulative	0	0	0	0	1	1	2	6	13	21	27	30	31	32	32	32
Percentage tumors ad libitum	0	0	0	0	2.04	2.04	4.16	12.5	27.2	43.8	56.3	62.5	64.6	66.6	66.6	66.6



will be seen that tumors first appeared in the fifth month and that the maximum frequency of appearance occurred during the tenth month of life.

Since 57 per cent of the restricted animals are alive at the sixteenth month, it is premature to speculate as to the eventual fate of these animals with respect to cancer incidence; however, they have survived six months, or about one third of the normal life span, beyond the time of maximum cancer incidence in their controls without the appearance of tumors in any animal. Furthermore, this has occurred on a diet which has increased the life span significantly. The differences in the mortality experience in the two groups are shown graphically in Fig. 2.

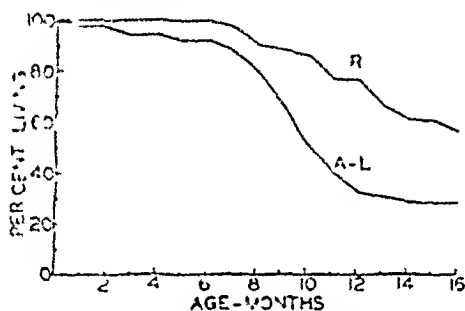


Fig. 2.—The percentage of C<sub>57</sub>H virgin female mice living at various ages. Curve A-L presents the values for the *ad libitum* diet. Curve R for the restricted diet.

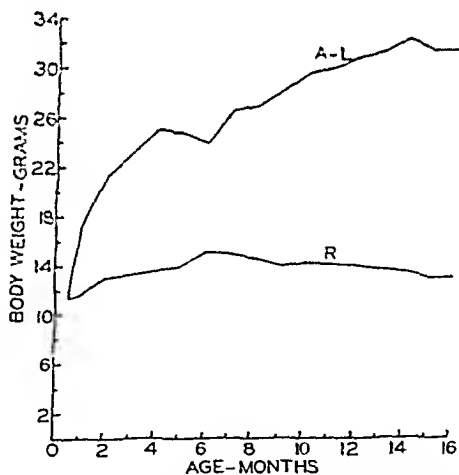


Fig. 3.—Mean body weights in relation to age of C<sub>57</sub>H virgin female mice. Curve A-L presents the values for the *ad libitum* diet. Curve R for the restricted diet.

It is reasonable to conclude from these data that a caloric dietary restriction which has improved the longevity of C<sub>57</sub>H female virgin mice has also reduced mammary cancer incidence at sixteen months from a control value of 67 per cent to zero in a significantly large series of animals. Mammary tumors may still occur at older ages in these mice

but eleven months have elapsed since the occurrence of the first tumor in the control series without tumor development in the restricted animals. This period is already nearly two-thirds of the usual life span.

**B. Growth.**—The mean body weights over time for the two groups of mice are shown in Fig. 3. The caloric restriction resulted in sharp limitation of weight increase. There is little or no visible fat in the restricted-diet mice. It is worthy of mention that the restricted-diet animals were much more active than the *ad libitum* group. The additional energy cost of exercise decreased the amounts of fat and carbohydrate available for body growth in the restricted animals and was therefore partly responsible for the low body weight. It is also interesting in this connection that a group of subline A strain mice maintained on the same restricted diet showed at age twelve months an average body weight 4 Gm. greater than did the C<sub>3</sub>H mice. The two strains showed identical mean body weights on *ad libitum* feeding. Obviously the two strains respond somewhat differently to dietary caloric restriction.

#### DISCUSSION

The reduction of spontaneous mammary carcinoma at age sixteen months from an incidence of 67 per cent in C<sub>3</sub>H virgins on *ad libitum* feeding to zero on a diet adequate in protein, vitamins, and minerals, which has been observed in this study, appears to prove that simple caloric restriction can greatly reduce the frequency of cancer during the usual period of maximum incidence. In all previous work caloric restriction has been complicated by simultaneous reduction in protein, vitamin, and salt intake, since the diets employed were identical in composition but different in amount in the full-fed and restricted groups. In such studies the reasonable possibility existed that a decrease in cancer incidence following food restriction was due to protein and vitamin deficiency rather than to caloric restriction. Furthermore, in no previous study have mice been caged individually and actual food intake of each animal controlled. When groups of mice are caged together, the more aggressive animals will obtain proportionately more food. Moreover, in previous studies on the effects of dietary restriction on spontaneous cancer incidence, commercially prepared animal feeds have been employed as part or all of the diets. Since their composition is uncontrollable, it seems advantageous to employ materials of known composition. The *ad libitum* diet used in this study gave appreciably more rapid growth than was obtained with purina fox chow.

The mechanism by which simple caloric restriction reduces spontaneous mammary cancer incidence is still obscure. Three known factors influence mammary cancer frequency in mice: (1) genetic susceptibility, (2) endocrine influence, and (3) milk factor (for literature see Snell, 1941, and Bittner, 1940). Factors 1 and 3 are known to be

present in the mice employed in this study. The adequacy of Factor 2, the endocrine influence, is uncertain under the conditions employed. The C.H strain was employed in this study after an attempt had been made to use A strain mice. The A strain shows high cancer incidence only in multiparous females. It was found that the restricted diet females were relatively infertile and only 37 per cent became pregnant, usually only once, on repeated exposure to males of known potency. None of these females became cancerous, a result which lends corroboration to the conclusion drawn from the present study. Nevertheless the result was unsatisfactory because the hormone factor had obviously not been controlled. The A strain females which were sterile while on the calorie-restricted diet became normally fertile within a few days after being placed on *ad libitum* feeding. There were, therefore, no irreversible changes produced by calorie restriction.

In the C.H strain the incidence of cancer is the same in virgin and parous females. This fact does not exclude the importance of a hormone influence. Nevertheless if such a factor exists it is supplied by the endocrine organs, presumably the ovaries, independent of pregnancy. It is possible that calorie restriction either decreases the production, increases the rate of destruction, or increases the threshold of sensitivity of breast tissue to the hormone involved. The evidence available at this time does not permit a final conclusion as to whether one of these changes actually occurs. However, studies are now under way designed to determine whether castrates given estrogenic materials parenterally show altered cancer incidence on restricted as compared with *ad libitum* diets, and also to ascertain the dose of estrogenic material necessary to maintain estrus on the two diets. Regarding the latter it can be said that no difference is apparent between the two groups as to sensitivity to estrogen.

Further studies on dietary restriction have been started in order to ascertain, among other facts, the latest period in the life span at which the institution of calorie reduction can significantly lower spontaneous cancer incidence. It is fully recognized that the degree and the time of diet restriction necessary to accomplish reduced cancer incidence are important questions in connection with the general problem, and especially in connection with any bearing which the results of animal experimentation may have upon the human cancer problem.

#### CONCLUSIONS

1. The incidence of spontaneous mammary carcinoma in C<sub>3</sub>H strain virgin female mice has been determined in relation to the calorie content of the diet, with the protein, vitamin, and salt intake approximately constant.

2. Restriction of carbohydrate and fat intake to accomplish a reduction of approximately one-third in total calories ingested resulted

in a change in mammary carcinoma incidence from 67 per cent in sixteen months in the controls to zero in the calorie-restricted mice.

3. The life span of the calorie-restricted mice was considerably increased over that of the fully fed controls.

4. Factors of possible importance in connection with these findings have been discussed.

#### REFERENCES

1. Bittner, John J.: Possible Method of Transmission of Susceptibility to Breast Cancer in Mice, *Am. J. Cancer* 39: 104-113, 1940.
2. Sivertsen, Ivar, and Hastings, Waldon H.: A Preliminary Report on the Influence of Food and Function on the Incidence of Mammary Gland Tumor in "A" Stock Albino Mice, *Minnesota Med.* 21: 873, 1938.
3. Snell, George D., editor: *Biology of the Laboratory Mouse*, Philadelphia, 1941, The Blakiston Co.
4. Tannenbaum, Albert: The Initiation and Growth of Tumors. I. Effects of Underfeeding, *Am. J. Cancer* 38: 335-350, 1940.

# EXPERIMENTAL STUDIES ON ALIMENTARY AZOTEMIA

## III. SITE OF BLOOD ABSORPTION\*

C. FRANK CHUSS, M.S., M.D., VICKSBURG, MISS.,  
HENRY N. HARRISS, M.D., PH.D., AND ROBERT T. BOALS, M.D.,  
DETROIT, MICH.

*(From the Division of General Surgery, the Vicksburg Clinic, Vicksburg, Miss.; and the Division of General Surgery, the Henry Ford Hospital, Detroit, Mich.)*

THE syndrome of alimentary azotemia and evidence<sup>1</sup> concerning its mechanism have been presented by us in previous publications.<sup>1, 2, 3</sup> These results were essentially in agreement with those of Sanghineti<sup>4</sup> and Schiff and his co-workers.<sup>5, 6</sup> Strong evidence was offered in support of the following conclusions: (1) Alimentary azotemia occurs in cases of massive hemorrhage into the intestinal tract, and this in turn most often results from a bleeding peptic ulcer. (2) The degree of the azotemia is of considerable prognostic significance, high blood urea nitrogen values being associated with high mortality. This is probably because the increase in blood urea nitrogen is a measure of the amount of blood lost. (3) The azotemia is due to absorption of digested blood and especially of its erythrocyte fraction (and in turn the latter's contained hemoglobin). (4) Finally, that since marked rises in blood urea nitrogen were also obtained following ingestion of protein, it seems as though the rise is probably due to and to a large extent proportional to the absorption of protein from the gastrointestinal tract.

The foregoing experiments were performed on the basis of blood introduced by stomach tube into the stomachs of experimental animals, and hence dealt primarily with blood in the stomach. A search of the literature revealed only one mention concerning alimentary azotemia occurring after absorption elsewhere than from the stomach or duodenum, although in various diseases large amounts of blood are lost into the lower portions of the gastrointestinal tract.

The only observations on this aspect of the subject prior to our own are those of Schiff and his associates<sup>6</sup> in 1939 on human beings. These authors fed blood into the fasting stomach through a Relfuss tube, and into the jejunum or upper ileum and colon through a Miller-Abbott tube. The maximum increase in the blood urea nitrogen was greater when the blood was introduced into the jejunum or upper ileum. After injection into the colon, no appreciable rise occurred. In clinical cases of bleeding into the colon, these authors observed no rise in the blood urea nitrogen.

Therefore it occurred to us to attempt to ascertain more precisely the site or sites in the gastrointestinal tract and ectopic sites, if any, in which after introduction of blood this phenomenon will occur.

\*All of the experimental work was performed at the Henry Ford Hospital, Detroit, Mich.

Received for publication, March 18, 1941.

## EXPERIMENTAL

**Method.**—Citrated whole beef blood and beef red blood cells were introduced in divided doses into the jejunum (two feet below Treitz' ligament) through a jejunostomy of the Maydl' type in two otherwise normal dogs. In a second set of two dogs, whole beef blood and beef red blood cells were introduced in divided doses low into the ileum (20 cm. proximal to the ileocecal valve), through an ileostomy of the Mann-Bollman<sup>8</sup> type. In additional experiments, one of the jejunostomy dogs and one of the low ileostomy dogs were given human red blood cells in a similar manner. In all, ten experiments were performed on four dogs.

Blood urea nitrogen determinations, using essentially the method of Van Slyke and Cullen<sup>9</sup> were made every four to six hours on each dog, from one to three days following the introduction of whole blood or of red blood cells by enterostomy into the respective levels of the small intestine. As in the previous experiments, the dogs were given their usual amount of food divided into four small meals daily. Water was given freely in the usual amounts. Daily hematocrit and hemoglobin determinations were made in six of the ten experiments revealing little change from the control level.

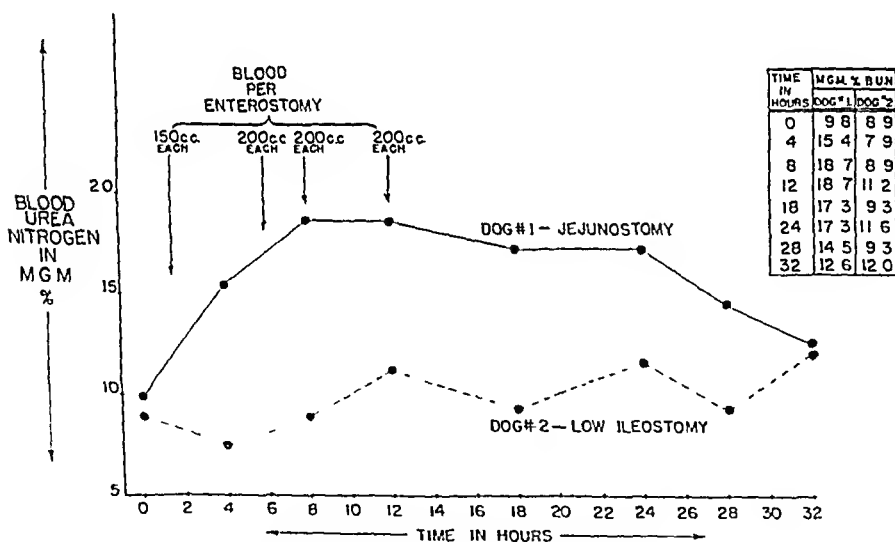


Fig. 1.—The effect of blood in the production of alimentary azotemia at different levels of the gastrointestinal tract of dogs.

**Results of Whole Blood Administration.**—As shown in Fig. 1, it was found that within three hours following the first dose of blood given into the jejunum, a marked rise in blood urea nitrogen occurred and the level continued on an elevated plane, as long as blood was given at short intervals. There was a return to a normal level of blood urea nitrogen within twenty-four hours following the introduction of the last dose of blood. In marked contrast to this curve is shown the nonelevated blood

# EXPERIMENTAL STUDIES ON ALIMENTARY AZOTEMIA

## III. SITE OF BLOOD ABSORPTION\*

C. FRANK CHESS, M.S., M.D., Vicksburg, Miss.,  
HENRY N. HARRIS, M.D., Ph.D., AND ROBERT T. BOALS, M.D.,  
DETROIT, MICH.

(From the Division of General Surgery, the Vicksburg Clinic, Vicksburg, Miss.; and the Division of General Surgery, the Henry Ford Hospital, Detroit, Mich.)

THE syndrome of alimentary azotemia and evidence<sup>1</sup> concerning its mechanism have been presented by us in previous publications.<sup>2,3,4</sup> These results were essentially in agreement with those of Sanguinetti<sup>5</sup> and Schiff and his co-workers.<sup>6,7</sup> Strong evidence was offered in support of the following conclusions: (1) Alimentary azotemia occurs in cases of massive hemorrhage into the intestinal tract, and this in turn most often results from a bleeding peptic ulcer. (2) The degree of the azotemia is of considerable prognostic significance, high blood urea nitrogen values being associated with high mortality. This is probably because the increase in blood urea nitrogen is a measure of the amount of blood lost. (3) The azotemia is due to absorption of digested blood and especially of its erythrocyte fraction (and in turn the latter's contained hemoglobin). (4) Finally, that since marked rises in blood urea nitrogen were also obtained following ingestion of protein, it seems as though the rise is probably due to and to a large extent proportional to the absorption of protein from the gastrointestinal tract.

The foregoing experiments were performed on the basis of blood introduced by stomach tube into the stomachs of experimental animals, and hence dealt primarily with blood in the stomach. A search of the literature revealed only one mention concerning alimentary azotemia occurring after absorption elsewhere than from the stomach or duodenum, although in various diseases large amounts of blood are lost into the lower portions of the gastrointestinal tract.

The only observations on this aspect of the subject prior to our own are those of Schiff and his associates<sup>8</sup> in 1939 on human beings. These authors fed blood into the fasting stomach through a Rehfuess tube, and into the jejunum or upper ileum and colon through a Miller-Abbott tube. The maximum increase in the blood urea nitrogen was greater when the blood was introduced into the jejunum or upper ileum. After injection into the colon, no appreciable rise occurred. In clinical cases of bleeding into the colon, these authors observed no rise in the blood urea nitrogen.

Therefore it occurred to us to attempt to ascertain more precisely the site or sites in the gastrointestinal tract and ectopic sites, if any, in which after introduction of blood this phenomenon will occur.

\*All of the experimental work was performed at the Henry Ford Hospital, Detroit, Mich.

Received for publication, March 18, 1941.

## EXPERIMENTAL

*Method.*—Citratd whole beef blood and beef red blood cells were introduced in divided doses into the jejunum (two feet below Treitz' ligament) through a jejunostomy of the Maydl<sup>7</sup> type in two otherwise normal dogs. In a second set of two dogs, whole beef blood and beef red blood cells were introduced in divided doses low into the ileum (20 cm. proximal to the ileocecal valve), through an ileostomy of the Mann-Bollman<sup>8</sup> type. In additional experiments, one of the jejunostomy dogs and one of the low ileostomy dogs were given human red blood cells in a similar manner. In all, ten experiments were performed on four dogs.

Blood urea nitrogen determinations, using essentially the method of Van Slyke and Cullen<sup>9</sup> were made every four to six hours on each dog, from one to three days following the introduction of whole blood or of red blood cells by enterostomy into the respective levels of the small intestine. As in the previous experiments, the dogs were given their usual amount of food divided into four small meals daily. Water was given freely in the usual amounts. Daily hematocrit and hemoglobin determinations were made in six of the ten experiments revealing little change from the control level.

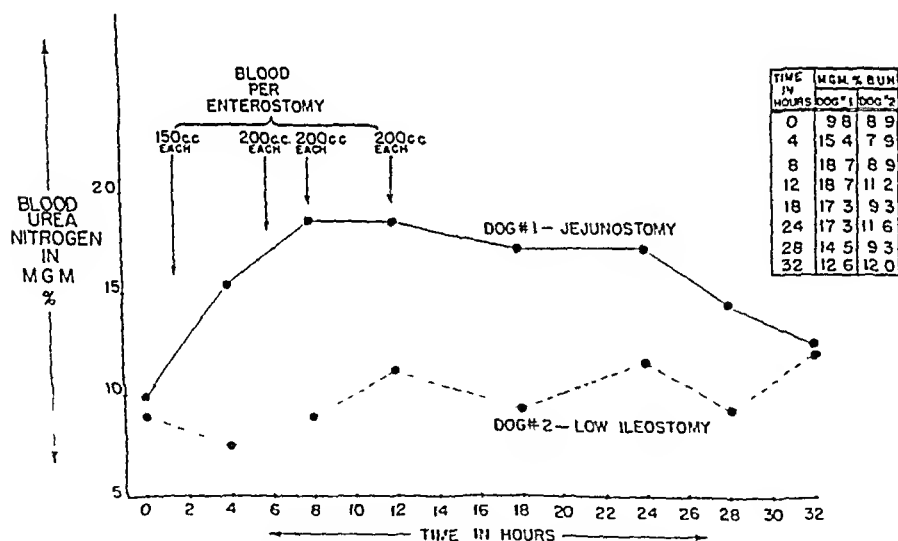


Fig. 1.—The effect of blood in the production of alimentary azotemia at different levels of the gastrointestinal tract of dogs.

*Results of Whole Blood Administration.*—As shown in Fig. 1, it was found that within three hours following the first dose of blood given into the jejunum, a marked rise in blood urea nitrogen occurred and the level continued on an elevated plane, as long as blood was given at short intervals. There was a return to a normal level of blood urea nitrogen within twenty-four hours following the introduction of the last dose of blood. In marked contrast to this curve is shown the nonelevated blood



urea nitrogen curve of the dog receiving the same amounts of blood at the same intervals and time into the lower portion of the ileum. Azotemia could not be produced by giving as much as 750 c.c. of whole blood into the lower ileum.

*Results of Blood Cells Administration.*—In four experiments, two dogs were given washed beef red blood cells by jejunostomy in divided doses, and in a second set of two dogs beef red blood cells, in identical amounts and intervals, were introduced into low ileostomies.

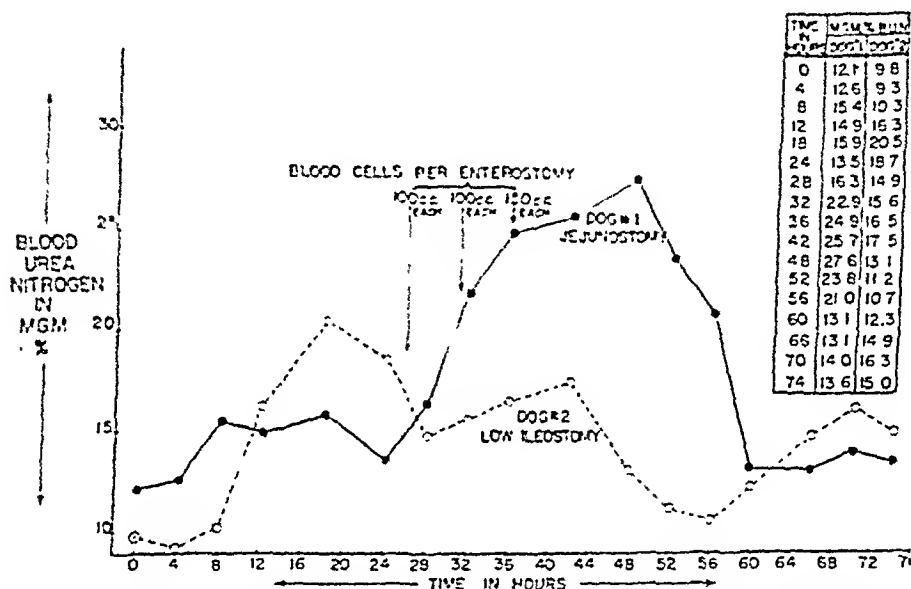


FIG. 2.—The effect of blood cells in the production of alimentary azotemia at different levels of the gastrointestinal tract of dogs.

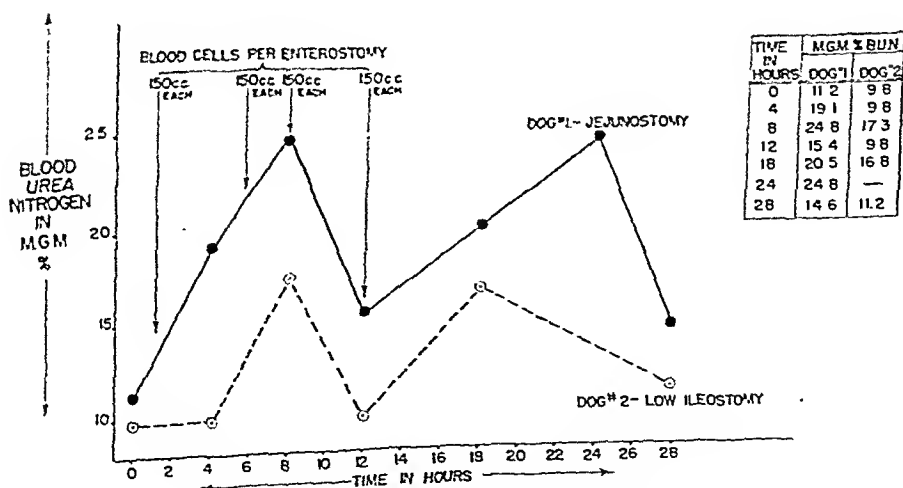


FIG. 3.—The effect of blood cells in the production of alimentary azotemia at different levels of the gastrointestinal tract of dogs.

As shown in Figs. 2 and 3, one of the animals receiving blood cells into the jejunum showed an initial elevation of blood urea nitrogen after one to two hours. Fig. 2 reveals the same type of curve in the jejunostomy animal as that for the animals following gastric ingestion of blood as previously reported.<sup>1, 2, 3</sup> However, it is to be noted that while the azotemia curves are of the same type, the degree of azotemia, though definitely abnormal, is possibly of a lesser degree for the same dosage of blood.

TABLE I

EFFECT OF BLOOD CELLS WHEN GIVEN AT DIFFERENT LEVELS OF GASTROINTESTINAL TRACT ON PRODUCTION OF ALIMENTARY AZOTEMIA IN DOGS

TIME IN HR.	MG. % BLOOD UREA NITROGEN	
	DOG 1 JEJUNOSTOMY	DOG 2 LOW ILEOSTOMY
0	11.2	9.8
1	Give each dog 150 c.c. blood cells per enterostomy	
4	19.1	9.8
6	Give each dog 150 c.c. blood cells per enterostomy	
8	Give each dog 150 c.c. blood cells per enterostomy	
8	24.8	17.3
12	Give each dog 150 c.c. blood cells per enterostomy	
12	15.4	9.8
18	20.5	16.8
24	24.8	—
28	14.6	11.2

In another experiment (Table I), the initial elevation of the blood urea nitrogen, in the jejunostomy animal, is to be noted, but this was followed by a fall to normal values in twelve hours followed by a second elevated peak in twenty-four hours, and a final return to normal four hours later. This drop of the twelve-hour reading is unexplained. In general, however, the results shown in Table I parallel those shown in Figs. 1 and 2.

Additional experiments were performed as follows: One of the ileostomy dogs was checked two months later and despite the administration of 600 c.c. beef red blood cells, no increase in blood urea nitrogen occurred. This same low ileostomy dog was also given human red blood cells on two occasions. In the first experiment, 500 c.c. human red blood cells given by ileostomy produced no effect. In the second experiment, after administration of 600 c.c. of human red blood cells by ileostomy the blood urea nitrogen rose from 14 to 24 mg. per cent. It was then found that this dog had received a single large feeding of meat just before this rise occurred which may have been a causative factor. One of the two jejunostomy dogs was given 600 c.c. human red blood cells into the jejunostomy with a resultant rise in the blood urea nitrogen level of from 8.5 to 25.7 mg. per cent.

*Results of Administration of Whole Blood Intraperitoneally.*—Three normal dogs were given respectively, 150 c.c., 200 c.c., 230 c.c. of citrated whole blood intraperitoneally, using aseptic technique. Blood urea nitrogen determinations were made every four to six hours for forty-

five hours following the introduction of blood. In Fig. 4 are seen the graphs of the three flat curves for these animals. No elevations of blood urea nitrogen above normal values were found throughout these experiments.

### SUMMARY

The administration of whole blood high into the jejunum of a dog produced an elevation of blood urea nitrogen with a return to normal levels in thirty-two hours, while the administration of identical amounts of whole blood low into the ileum caused no elevation of blood urea nitrogen.

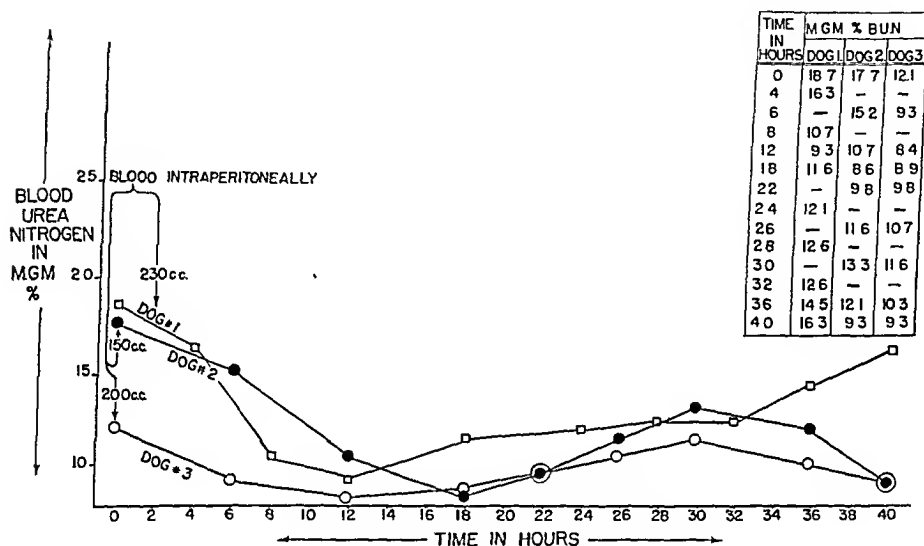


Fig. 4.—No azotemia is shown following administration of blood intraperitoneally in dogs.

Two dogs were given blood cells high into the jejunum with resulting azotemia for periods of twenty-seven and thirty-four hours respectively. Two dogs were given identical amounts of blood cells low into the ileum without a resultant elevation of the blood urea nitrogen.

Three experiments were performed in which three dogs were given whole blood intraperitoneally without producing azotemia in the succeeding forty hours.

Correlation of these results with those previously reported showing that azotemia results from the intragastric administration of blood would indicate that to produce alimentary azotemia, blood must be present in the upper half of the alimentary tract. This conclusion, in turn, is capable of two interpretations: (1) that unless the blood is present in the upper portion of the intestinal tract, it is not absorbed in sufficient quantities to produce alimentary azotemia; or (2) that the blood must be digested in the upper portion of the gut to produce substances which, when absorbed, will produce alimentary azotemia.

Our results cannot give a conclusive answer as to which of these conclusions is more correct. We were, however, able to show that a 5 per cent urea solution produced as marked a rise in blood urea nitrogen when introduced into the stoma of one of our low ileostomy dogs as when introduced into one of the jejunostomy dogs. These results are shown in Fig. 5. Other experiments with predigested blood or red blood cells might have given the same or another result, but they were not performed.

At any rate, our experiments indicate that an appreciable alimentary azotemia results only when blood is present in the upper intestinal tract. This observation has an especial clinical application to cases of intestinal hemorrhage.

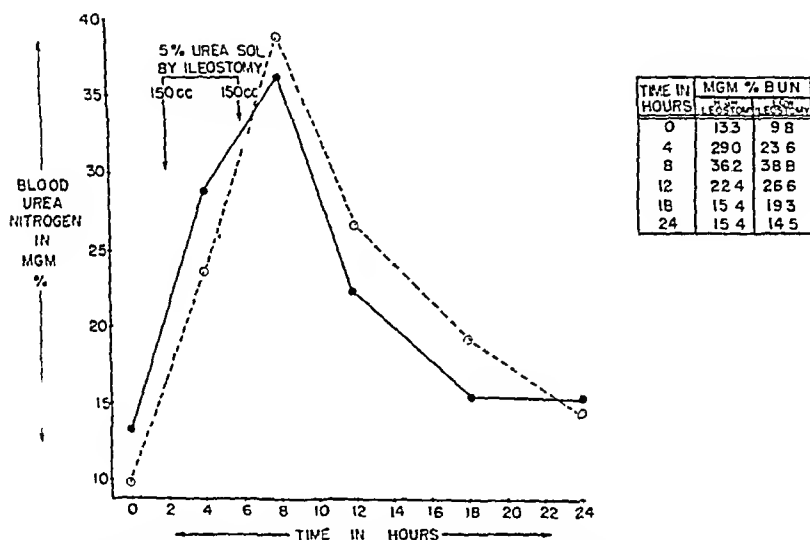


Fig. 5.—The comparative effects of a 5 per cent urea solution in the production of alimentary azotemia in high and low ileostomy dogs. The solid line represents the results in the dog with a high jejunostomy, while the broken line represents the results in the dog with a low ileostomy.

### CONCLUSIONS

1. Alimentary azotemia occurs in the experimental animal (dog) following the intrajejunal administration of whole blood or red blood cells. The degree of azotemia, although definite, is somewhat less than that produced by the intragastric administration of similar amounts of whole and blood cells.

2. Whole blood and blood cells introduced low into the ileum produce much less azotemia than when similar amounts are introduced higher up into the intestinal tract.

3. Whole blood in the peritoneal cavity of experimental animals (dogs) produces no azotemia.

five hours following the introduction of blood. In Fig. 4 are seen the graphs of the three flat curves for these animals. No elevations of blood urea nitrogen above normal values were found throughout these experiments.

### SUMMARY

The administration of whole blood high into the jejunum of a dog produced an elevation of blood urea nitrogen with a return to normal levels in thirty-two hours, while the administration of identical amounts of whole blood low into the ileum caused no elevation of blood urea nitrogen.

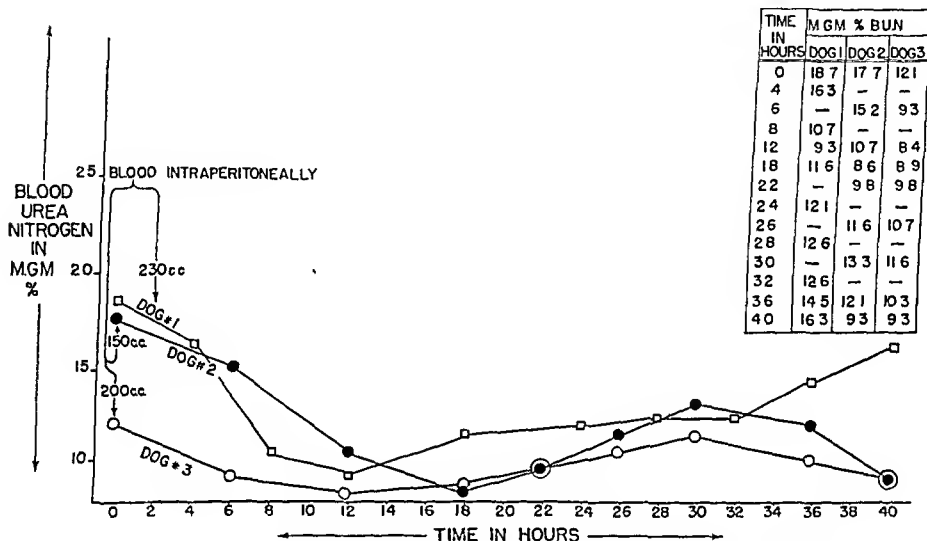


Fig. 4.—No azotemia is shown following administration of blood intraperitoneally in dogs.

Two dogs were given blood cells high into the jejunum with resulting azotemia for periods of twenty-seven and thirty-four hours respectively. Two dogs were given identical amounts of blood cells low into the ileum without a resultant elevation of the blood urea nitrogen.

Three experiments were performed in which three dogs were given whole blood intraperitoneally without producing azotemia in the succeeding forty hours.

Correlation of these results with those previously reported showing that azotemia results from the intragastric administration of blood would indicate that to produce alimentary azotemia, blood must be present in the upper half of the alimentary tract. This conclusion, in turn, is capable of two interpretations: (1) that unless the blood is present in the upper portion of the intestinal tract, it is not absorbed in sufficient quantities to produce alimentary azotemia; or (2) that the blood must be digested in the upper portion of the gut to produce substances which, when absorbed, will produce alimentary azotemia.

# PILONIDAL SINUSES OCCURRING OVER THE HIGHER SPINAL SEGMENTS WITH REPORT OF A CASE INVOLVING THE SPINAL CORD

HENRY P. KOOISTRA, M.D., M.S. (SURG.), GRAND RAPIDS, MICH.

(From the Department of Surgery, University Hospital, Ann Arbor, Mich.)

PILONIDAL sinuses are rarely encountered over spinal segments higher than the sacrococcygeal region. A review of the literature reveals only thirteen cases previously reported. These usually revealed a sinus communicating between the skin surface and the meninges, but in no case was the lesion found actually to invade the substance of the spinal cord. In the case about to be presented, the lesion was shown at operation to be intramedullary. The mouth of the sinus presented itself over the upper margin of the third thoracic vertebra.

The lesions, as found over the higher spinal segments, present a microscopic pathologic picture quite identical with that of pilonidal sinuses occurring in the sacrococcygeal region. Clinically, however, the former are more serious because of their location over the spinal cord and its coverings. In this location, any infection of these sinuses is prone to be carried to the meninges. Furthermore, even in the absence of infection, sufficient pressure may be exerted by the lesion to produce compression of the cord elements and result in signs and symptoms typical of a cord tumor. The early recognition of this lesion at any level of the spine is essential to proper treatment. Surgical removal carries an excellent prognosis.

## REVIEW OF LITERATURE

In Fig. 1 is shown the site of the unusually located pilonidal sinuses of the present case and those collected from the literature. An abstract of these cases is given as follows.

Clark<sup>2</sup> was the first to report a pilonidal sinus-like lesion occurring at a site away from the sacrococcygeal region. His case, a 13-year-old girl, had a small hair-containing sinus in the median line, between the spinous processes of the fourth and fifth cervical vertebrae. On examination she showed a lack of manual dexterity and an incapacity for work requiring finer movements of the fingers and hands. Roentgenograms were negative but for a demonstrable cleft in the arch of the third cervical vertebra. The lesion was not confirmed by either operation or necropsy.

Moise<sup>11</sup> reported the first proved case. His patient, a male aged 18 years, had a congenital discharging pilonidal sinus in the lower lumbar

## REFERENCES

1. Chunn, C. F., and Harkins, H. N.: Alimentary Azotemia Due to Whole Blood Absorption From the Gastro-intestinal Tract, *Proc. Soc. Exper. Biol. & Med.* 45: 569-571, 1940.
2. Chunn, C. F., and Harkins, H. N.: Experimental Studies on Alimentary Azotemia. I. The Role of Blood Absorption From the Gastro-intestinal Tract, *SURGERY* 9: 695-705, 1941.
3. Chunn, C. F., and Harkins, H. N.: Experimental Studies on Alimentary Azotemia. II. The Relative Importance of the Plasma and Erythrocyte Fraction of Absorbed Blood, *SURGERY* 10: 991, 1941.
4. Sanguinetti, Lucio V.: Azoemias en el curso de las hemorragias retenidas a nivel del tubo digestivo (estudio clínico y experimental), *Arch. argent. de enferm. d. ap. digest. y de la nutrición* 9: 264-287, 1934.
5. Schiff, L., and Stevens, R. J.: Elevation of Urea Nitrogen Content of the Blood Following Hematemesis or Melena, *Arch. Int. Med.* 64: 1239-1251, 1939.
6. Schiff, L., Stevens, R., Goodman, S., Garber, E., and Lublin, A.: Observations on the Oral Administration of Citrated Blood in Man, *Am. J. Digest. Dis.* 6: 597-602, 1939.
7. Maydl: Cited by Markowitz, J.: *Textbook of Experimental Surgery*, Baltimore, 1937, William Wood & Co.
8. Mann, F. C., and Bollman, J.: A Method for Making a Satisfactory Fistula at Any Level of the Gastro-Intestinal Tract, *Ann. Surg.* 13: 794-797, 1931.
9. Van Slyke, D. D., and Cullen, G. E.: In Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, 1932, Williams and Wilkins Co., vol. 2, p. 547.

vesicorectal incontinence. Roentgenograms revealed a rachischisis of the second thoracic vertebra, and a myelogram demonstrated a block at this level. At operation the sinus was found to communicate with a dermoid cyst which lay beneath the arachnoid. The cyst measured about 6.5 by 2 cm. and was filled with hair and sebaceous material. Following surgery the patient made a complete recovery but for a residual weakness of the lower extremities.

Hipsley<sup>9</sup> reported a case, a female, 3 years of age, who developed difficulty in walking four weeks prior to admission. She presented a discharging midline sinus over the first thoracic spine. This sinus was hair containing and the area about its orifice was indurated. The spinal fluid was xanthochromic, with 72 cells per cubic millimeter; lymphocytes, 80 per cent; neutrophils, 20; no organisms. A myelogram showed an arrest of the lipiodol at the seventh cervical vertebra. At operation a sinus over the spine of the second dorsal vertebra was found to be bifid, and through perforation at its base the sebaceous material of the cyst was seen extrude. Lying subdurally and attached to the dura was a dermoid cyst, 18 by 12 mm., which was removed. Following surgery there was nearly a complete recovery.

Walker and Buey<sup>16</sup> in an excellent article on congenital dermal sinuses stressed the fact that these sinuses extend to the meninges and that infection of such a lesion is prone to produce either a spinal meningitis or a subdural abscess. They presented three new cases. The first case was that of a 5-year-old female, who developed symptoms at 18 months of age, and on whom a diagnosis of tuberculous meningitis was made at that time. This child, four and one-half years later, was found to have a congenital sinus over the fourth thoracic vertebra. Roentgenograms of this area showed an incomplete fusion of its laminae. At operation, the spinous process of this vertebra was found to be absent, and following a laminectomy, an inflammatory mass composed of numerous small sterile abscesses was excised from beneath the thickened dura. Postoperatively, the patient went on to an uneventful complete recovery. Their second case was a female, aged 3 years, with a similar lesion over the fourth lumbar vertebra, on whom a diagnosis of tuberculous meningitis had likewise been made. Roentgenograms showed an incomplete fusion of the laminae of the sacral segments, while the lumbar vertebrae were apparently normal. At operation, the sinus was seen passing between the fourth and fifth lumbar vertebrae down to the dura, to which it was firmly attached. Following laminectomy and incision of the dura, a small cystic cavity was encountered which was filled with thick creamy pus, and some sebaceous material. The abscess extended from the level of the fifth lumbar inferiorly to about the level of the twelfth thoracic vertebra superiorly, where a hole was noted in the floor of the abscess cavity. The wound was closed with drainage and her recovery was satisfactory.



region. This became infected and produced a staphylococcus meningitis. At operation the sinus was found to extend through a bony defect at the junction of the first and second sacral vertebrae and to communicate with the subarachnoid space. A laminectomy was performed, the sinus and its granulation tissue excised, and the wound drained. The patient then went on to an uneventful and complete recovery.

Ripley and Thompson<sup>13</sup> reported quite a similar case two years later in a 3½-month-old male infant, who developed a fatal staphylococcus meningitis secondary to infection of a congenital pilonidal sinus. At operation the sinus was found to pass into the sacral canal, in the region of the second sacral arch, which was found to be absent. The sac removed at operation was found to contain a hair and sebaceous material.

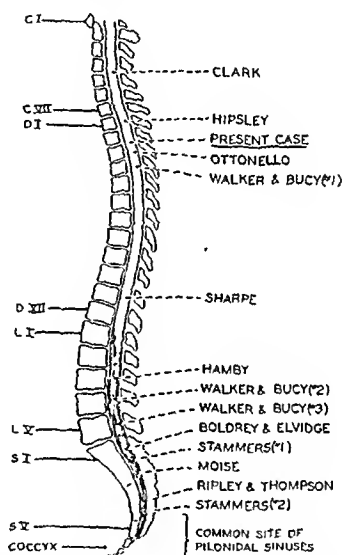


Fig. 1.—A diagram illustrating the higher spinal levels at which were found the pilonidal sinuses reported by the various authors.

W. Sharpe and N. Sharpe<sup>14</sup> reported a case of a male aged 3 years, with a congenital pinhead-sized depression over the lower thoracic region which drained purulent material intermittently. His back was rigid, and prior to operation he developed a spastic paralysis of both legs. Roentgenograms demonstrated a failure of fusion in the left lamina of the eleventh dorsal vertebra. At operation, a laminectomy was performed, and a fibrous mass containing hair and caseous material was removed from between the dura and the spinal cord. His convalescence was uneventful and the subsequent recovery nearly complete.

Ottonello<sup>12</sup> reported a case in a female, aged 20 years. She had a minute sinus over the third dorsal vertebra. Two weeks prior to hospital admission she developed a paraplegia, sensory symptoms, and a

vesicorectal incontinence. Roentgenograms revealed a rachischisis of the second thoracic vertebra, and a myelogram demonstrated a block at this level. At operation the sinus was found to communicate with a dermoid cyst which lay beneath the arachnoid. The cyst measured about 6.5 by 2 cm. and was filled with hair and sebaceous material. Following surgery the patient made a complete recovery but for a residual weakness of the lower extremities.

Hipsley<sup>9</sup> reported a case, a female, 3 years of age, who developed difficulty in walking four weeks prior to admission. She presented a discharging midline sinus over the first thoracic spine. This sinus was hair containing and the area about its orifice was indurated. The spinal fluid was xanthochromic, with 72 cells per cubic millimeter; lymphocytes, 80 per cent; neutrophils, 20; no organisms. A myelogram showed an arrest of the lipiodal at the seventh cervical vertebra. At operation the spine of the second dorsal vertebra was found to be bifid, and through a perforation at its base the sebaceous material of the cyst was seen to extrude. Lying subdurally and attached to the dura was a dermoid cyst, 18 by 12 mm., which was removed. Following surgery there was nearly a complete recovery.

Walker and Buey<sup>10</sup> in an excellent article on congenital dermal sinuses stressed the fact that these sinuses extend to the meninges and that infection of such a lesion is prone to produce either a spinal meningitis or a subdural abscess. They presented three new cases. Their first case was that of a 5-year-old female, who developed symptoms at 6 months of age, and on whom a diagnosis of tuberculous meningitis was made at that time. This child, four and one-half years later, was found to have a congenital sinus over the fourth thoracic vertebra. Roentgenograms of this area showed an incomplete fusion of its laminae. At operation, the spinous process of this vertebra was found to be absent, and following a laminectomy, an inflammatory mass composed of numerous small sterile abscesses was excised from beneath the thickened dura. Postoperatively, the patient went on to an uneventful complete recovery. Their second case was a female, aged 3 years, with a similar lesion over the fourth lumbar vertebra, on whom a diagnosis of tuberculous meningitis had likewise been made. Roentgenograms showed an incomplete fusion of the laminae of the sacral segments, while the lumbar vertebrae were apparently normal. At operation, the sinus was seen passing between the fourth and fifth lumbar vertebrae down to the dura, to which it was firmly attached. Following laminectomy and incision of the dura, a small cystic cavity was encountered which was filled with thick, creamy pus, and some sebaceous material. The abscess extended from the level of the fifth lumbar inferiorly, to about the level of the twelfth thoracic vertebra superiorly, where a hole was noted in the floor of the abscess cavity. The wound was closed with drainage and her recovery was satisfactory.

The third case presented by Walker and Buey was one operated upon some years previously by Dr. D. B. Phemister. The patient, a colored female, aged 3 years, presented a hairy pigmented area over the fifth lumbar spine, and in the center of this there was a minute sinus. Roentgenograms showed a failure of fusion of the spinous processes of the fifth lumbar and first sacral vertebrae. At operation, the sinus was found to pass through a defect in the spinous process of the fifth lumbar vertebra to a subdural inflammatory sac. This contained a few drops of glairy, gelatinous, slightly purulent material. The postoperative course was uneventful.

Hamby<sup>7</sup> reported a case exhibiting a pilonidal cyst, not communicating with the skin, associated with multiple other congenital abnormalities of the spine and cord. The patient, a white female, aged 20 years, was born with a midline dimple over the lumbar spine. About this a profuse growth of hair occurred in later years. She complained of back pain and difficulty in walking. Roentgenograms showed a failure of fusion of the laminae of the last three lumbar vertebrae, with an associated fusion of the bodies of the fourth and fifth. At operation, a tumor was exposed at about the level of the third and fourth lumbar vertebrae, which upon being incised revealed a sac containing fluid under pressure and a mass of curly hair. The deeper part of this pilonidal cyst was attached to a bony exostosis which arose from the anterior wall of the spinal canal. The spinal cord was seen to become bifid at this level and was noted to be longer than usual. Following operation with removal of the cyst, the patient made an uneventful recovery.

Stammers<sup>15</sup> reported two quite identical cases, in each of which the patient made an uninterrupted and apparently complete recovery following surgery. The first case was that of a male, aged 2 years, who developed symptoms six weeks prior to admission. He showed ease of fatigue, irritability, and difficulty in walking. Examination revealed a small sinus over the upper sacrum. From this sinus a fibrous cord could be felt running beneath the skin upward to the lumbosacral junction. This area was tender, and the spine was held rigid. Roentgenograms disclosed a spina bifida of the fifth lumbar vertebra. The spinal fluid was turbid, contained 426 cells (unspecified) per cubic millimeter, and showed numerous *Staphylococcus albus* organisms. At operation the sinus was found to communicate through the spina bifida with a large dermoid cyst lying within the spinal canal. The second case, a male aged 4 years, presented a discharging congenital sinus over the lower sacrum. Two weeks prior to admission, he began to complain of headaches and pain in the lower back, had vomited and shown a fever. Examination revealed a hyperextended spine, retracted head, neck rigidity, spasticity of the arms, and the knees drawn upward. There was a bilateral Kernig sign. Lumbar puncture produced "a few drops of thick ropy pus" from which "coliform bacilli and enterococci" were recovered. Repeated

cisterna puncture produced a sterile cerebrospinal fluid. At operation the sacral canal was explored and the cavity found to contain thick pus. The sinus was found to be attached to the dura mater of the cord.

Boldrey and Elvidge<sup>1</sup> have reported the most recent case. Their patient, a boy  $2\frac{1}{2}$  years of age, had a congenital sinus over the lumbosacral spine which had drained intermittently for nine months. For five months he had periodic attacks of chills, fever, opisthotonos and vomiting. On admission he held his knees drawn up and showed a neck stiffness. At operation the sinus was found to pass through a bifid fifth lumbar vertebra, and to communicate with an infected dermoid cyst lying subdurally. The cyst extended from the twelfth dorsal to the second sacral vertebra and was intimately adherent to many roots of the cauda equina. It contained sebaceous material, hair, and pus. Following a prolonged stormy convalescence the patient made a good recovery.

#### REPORT OF A CASE\*

D. D. C., a white, male student, aged 19 years, entered the University Hospital, on May 7, 1936. His chief complaint was that of "difficulty in walking." He first developed symptoms thirteen years previously when he experienced a "limp" in his right leg while convalescing from an attack of measles. From May through August, 1923, the limp remained apparently stationary, and then a gradual improvement was noted. However, in November, following an attack of chicken pox, there was such a marked exacerbation of the symptoms that walking became an impossibility. Two months later, when he was again able to walk, the left foot began to trouble him for the first time. He was informed by his mother that he then walked with his legs crossed "like a pair of scissors," and that he had a marked "trembling of his feet" (probably a clonus).

The following April he entered a large metropolitan hospital for a thorough case study. Examination here revealed a dimple with a small tuft of hair in the region of the third dorsal spine. His mother stated she had noticed this dimple since early childhood. Roentgenograms of this region were taken and reported to be normal. Spinal fluid examination revealed 15 W.B.C. (unspecified) per cubic millimeter, 1+ globulin, and mastic 331000000. No definite diagnosis was made on two visits, however, and no specific therapy was instituted.

A gradual decrease in symptoms was noted during ensuing months, and after one year a fair recovery was made. There was then only a mild stiffness and some weakness of the legs, upon prolonged exercise. He was able to resume school life and take an active part in both basketball and football. Periodically the dimple over his spine produced soreness in the shoulder region and back. On one occasion the soreness was relieved when his mother extracted the hair. On a subsequent recurrence of this trouble, the mother removed the hair early to obviate further soreness, but this time it only served to aggravate the pain. Hair was removed from the dimple last about four years ago.

Two years prior to the present admission, following an outing at which he became very fatigued, there was a recurrence of the symptoms. This time the left foot was the first to become involved. The condition grew progressively worse until three months before admission when the right foot also became involved. This forced him to drop his college work, as he was able to walk only about twelve to fifteen feet

\*This case is also referred to in a current publication by Dr. Carl List on "Dermoids of the Spinal Cord."

The third case presented by Walker and Bucy was one operated upon some years previously by Dr. D. B. Phemister. The patient, a colored female, aged 3 years, presented a hairy pigmented area over the fifth lumbar spine, and in the center of this there was a minute sinus. Roentgenograms showed a failure of fusion of the spinous processes of the fifth lumbar and first sacral vertebrae. At operation, the sinus was found to pass through a defect in the spinous process of the fifth lumbar vertebra to a subdural inflammatory sac. This contained a few drops of glairy, gelatinous, slightly purulent material. The postoperative course was uneventful.

Hamby<sup>7</sup> reported a case exhibiting a pilonidal cyst, not communicating with the skin, associated with multiple other congenital abnormalities of the spine and cord. The patient, a white female, aged 20 years, was born with a midline dimple over the lumbar spine. About this a profuse growth of hair occurred in later years. She complained of back pain and difficulty in walking. Roentgenograms showed a failure of fusion of the laminae of the last three lumbar vertebrae, with an associated fusion of the bodies of the fourth and fifth. At operation, a tumor was exposed at about the level of the third and fourth lumbar vertebrae, which upon being incised revealed a sac containing fluid under pressure and a mass of curly hair. The deeper part of this pilonidal cyst was attached to a bony exostosis which arose from the anterior wall of the spinal canal. The spinal cord was seen to become bifid at this level and was noted to be longer than usual. Following operation with removal of the cyst, the patient made an uneventful recovery.

Stammers<sup>15</sup> reported two quite identical cases, in each of which the patient made an uninterrupted and apparently complete recovery following surgery. The first case was that of a male, aged 2 years, who developed symptoms six weeks prior to admission. He showed ease of fatigue, irritability, and difficulty in walking. Examination revealed a small sinus over the upper sacrum. From this sinus a fibrous cord could be felt running beneath the skin upward to the lumbosacral junction. This area was tender, and the spine was held rigid. Roentgenograms disclosed a spina bifida of the fifth lumbar vertebra. The spinal fluid was turbid, contained 426 cells (unspecified) per cubic millimeter, and showed numerous *Staphylococcus albus* organisms. At operation the sinus was found to communicate through the spina bifida with a large dermoid cyst lying within the spinal canal. The second case, a male aged 4 years, presented a discharging congenital sinus over the lower sacrum. Two weeks prior to admission, he began to complain of headaches and pain in the lower back, had vomited and shown a fever. Examination revealed a hyperextended spine, retracted head, neck rigidity, spasticity of the arms, and the knees drawn upward. There was a bilateral Kernig sign. Lumbar puncture produced "a few drops of thickropy pus" from which "coliform bacilli and enterococci" were recovered. Repeated

eisterna puncture produced a sterile cerebrospinal fluid. At operation the sacral canal was explored and the cavity found to contain thick pus. The sinus was found to be attached to the dura mater of the cord.

Boldrey and Elvidge<sup>1</sup> have reported the most recent case. Their patient, a boy 2½ years of age, had a congenital sinus over the lumbosacral spine which had drained intermittently for nine months. For five months he had periodic attacks of chills, fever, opisthotonos and vomiting. On admission he held his knees drawn up and showed a neck stiffness. At operation the sinus was found to pass through a bifid fifth lumbar vertebra, and to communicate with an infected dermoid cyst lying subdurally. The cyst extended from the twelfth dorsal to the second sacral vertebra and was intimately adherent to many roots of the cauda equina. It contained sebaceous material, hair, and pus. Following a prolonged stormy convalescence the patient made a good recovery.

#### REPORT OF A CASE<sup>2</sup>

D. D. C., a white, male student, aged 19 years, entered the University Hospital, on May 7, 1936. His chief complaint was that of "difficulty in walking." He first developed symptoms thirteen years previously when he experienced a "hump" in his right leg while convalescing from an attack of measles. From May through August, 1923, the hump remained apparently stationary, and then a gradual improvement was noted. However, in November, following an attack of chicken pox, there was such a marked exacerbation of the symptoms that walking became an impossibility. Two months later, when he was again able to walk, the left foot began to trouble him for the first time. He was informed by his mother that he then walked with his legs crossed "like a pair of scissors," and that he had a marked "trembling of his feet" (probably a clonus).

The following April he entered a large metropolitan hospital for a thorough case study. Examination here revealed a dimple with a small tuft of hair in the region of the third dorsal spine. His mother stated she had noticed this dimple since early childhood. Roentgenograms of this region were taken and reported to be normal. Spinal fluid examination revealed 15 W.B.C. (unspecified) per cubic millimeter, 1+ globulin, and mastic 33100000. No definite diagnosis was made on two visits, however, and no specific therapy was instituted.

A gradual decrease in symptoms was noted during ensuing months, and after one year a fair recovery was made. There was then only a mild stiffness and some weakness of the legs, upon prolonged exercise. He was able to resume school life and take an active part in both basketball and football. Periodically the dimple over his spine produced soreness in the shoulder region and back. On one occasion the soreness was relieved when his mother extracted the hair. On a subsequent recurrence of this trouble, the mother removed the hair early to obviate further soreness, but this time it only served to aggravate the pain. Hair was removed from the dimple last about four years ago.

Two years prior to the present admission, following an outing at which he became very fatigued, there was a recurrence of the symptoms. This time the left foot was the first to become involved. The condition grew progressively worse until three months before admission when the right foot also became involved. This forced him to drop his college work, as he was able to walk only about twelve to fifteen feet

<sup>1</sup>This case is also related to in a current publication by Dr. Carl List on "Dermoids of the Spinal Cord."

without resting his legs. His difficulty has been concerned primarily with locomotion, and he was entirely free from pain. Recently, however, he has become constipated and experienced some difficulty in initiating urination.

The past history revealed no other illnesses than those described above. The family history was significant only so far as it revealed a brother who had a "cyst removed from the end of the spine." This was diagnosed to be a pilonidal cyst.



Fig. 2.—Iodized oil, cave upper pedicles in taken with the patient in a 60° Trendelenburg position. The coid at the level of the third dorsal vertebra, has a coid tumor. There is a noticeable thinning of the al region, when compared with those on the right.

Physical examination revealed a well developed and well nourished young adult male who walked with great difficulty. At the level of the upper border of the third dorsal spinous process there was a midline sinus, about 1 mm. in diameter, with several hairs protruding from it, a typical pilonidal sinus. There was marked tenderness on pressure over the region of the second dorsal process, and just to the right of this a small deep-seated tumor mass could be felt. The remainder of the examination was negative but for the following neurologic findings. There was a paresis of the intercostal muscles on the left, below the level of the third interspace, as well as the left abdominal muscles. The abdominal reflexes were absent except for a weak response in the right upper quadrant. There was a spastic paraparesis of the legs, most marked on the left. The left foot was held in a equinovarus position. The knee and Achilles jerks were markedly hyperactive. There was an abortive ankle clonus bilaterally, most marked on the left. There were also bilateral

Babinski, Schaffer, Chaddock and Oppenheim signs. There was hypalgesia on the legs but no analgesia. Vibratory sense was lost in both ankles and absent in the left knee but present in the right. Position sense of the toes was lost on the left and impaired on the right. There was a positive Romberg sign. The gait was that of the spastic ataxic type.

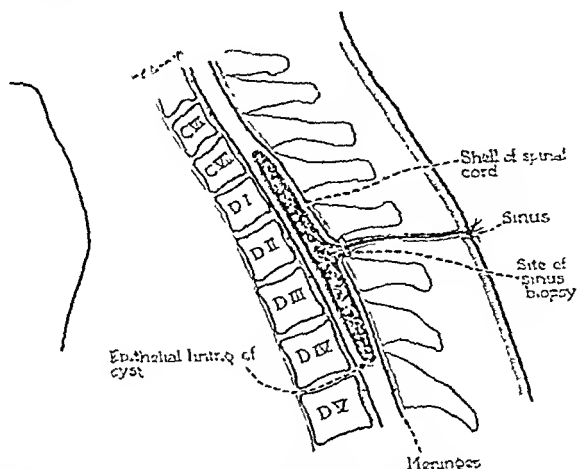


Fig. 3.—Mid-sagittal section showing diagrammatically the considerable vertical extent of the lesion. Note that the sinus passes between the spinous processes of the second and third dorsal vertebrae.

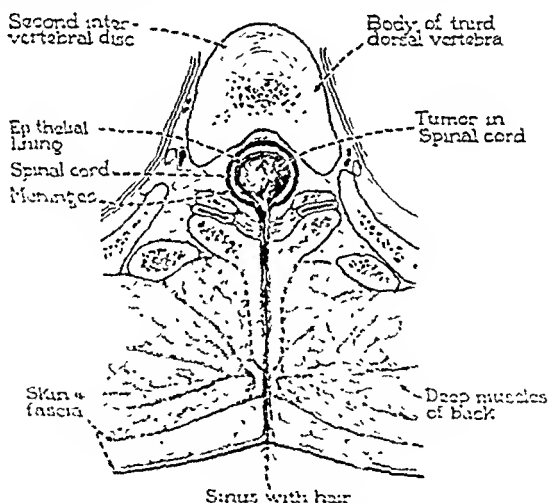


Fig. 4.—Cross section showing diagrammatically the lesion within the cord. Note that only a thin shell of spinal cord tissue is left about the tumor. The relation of the central canal of the cord to the lesion could not be determined.

Lumbar puncture done in the supine position showed an initial pressure of 165 mm. of water, but this dropped to 0 after the removal of 4 c.c. of fluid. The spinal fluid had an xanthochromic color and was clear. Testing for a spinal fluid block, one noted a good response on coughing, and a fair response on straining, while compression of the jugular veins produced a very slow rise of only a few millimeters with a similar fall.

*Laboratory Studies.* The spinal fluid gave a positive carboic acid and Nonne-Apert reaction. Microscopic study revealed only red blood cells, probably due to



venepuncture. The Kahn test was negative; colloidal gold curve, 0221233210; mastic, 123321. The blood Kahn test was also negative, and routine blood and urine studies were essentially normal.

*Roentgenograms* of the spine revealed a widening of the spinal canal in the upper thoracic region, with an apparent thinning of the left pedicles of the first three or four vertebrae. There was a *spina bifida occulta* of the sacrum. A myelogram was undertaken, with 1 c.c. of iodized oil injected into the spinal canal in the lumbar region. The roentgenograms, shown in Fig. 2, with the patient in a 60° Trendelenburg position, revealed an abrupt stoppage of the oil at the level of the third dorsal vertebra. The upper margin of the oil column exhibited a concave pattern. These findings were considered to be diagnostic of a cord tumor.

*Operation.*—On May 11, 1936, under avertin anesthesia, Dr. Max M. Peet performed a cervical-dorsal laminectomy on the patient. An incision was made from the seventh cervical to the fourth dorsal vertebra. While stripping away the muscles, the dermal sinus was seen to extend down to the spine. The spinous processes and laminae of the last cervical and upper four dorsal vertebrae were removed, exposing the dura. This was covered by a very scant amount of epidural fat. The sinus was found to be connected to the meninges in the interspace between the second and third dorsal spinous processes. Upon opening the dura, and incising what appeared to be a thinned-out spinal cord, a large mass of sebaceous material containing a great number of hairs was encountered. This was removed by curettement. All of this material was intramedullary and only a shell of the spinal cord remained. Figs. 3 and 4 diagram these findings. The tumor was about 4 inches long, extending from the seventh cervical to the fourth dorsal vertebra. No attempt was made to close the dura, and the wound was closed without a drain.



Fig. 5.—A high-power photomicrograph of curetted intramedullary tissue showing stratified squamous epithelium and sebaceous glands.

*Pathologic Report.*—Curettement of the cavity within the cord produced a fragment of tissue which was lined by a stratified squamous epithelium with associated hairs and sebaceous glands (Fig. 5). Microscopically the extradural sinus showed a tract of vascular pyrogenic granulation tissue. In this there was a cordlike structure with a central lumen lined by stratified squamous epithelium and showing numerous hair shafts and sebaceous glands. This presented the picture of a pilonidal sinus. A cross section of this lesion taken just superficial to the cord showed

the sinus and granulation tissue surrounded with meningeal coverings and exhibiting numerous psammoma bodies (Figs. 6 and 7). Culture of the cyst contents was negative for growth.

*Course in Hospital.*—The patient's condition postoperatively was excellent after the first two days. He developed a mild urinary incontinence which required catheterization for ten days. His temperature returned to normal by the ninth postoperative day, at which time the skin sutures were removed. He was permitted up on the sixteenth day and was discharged about two weeks later.

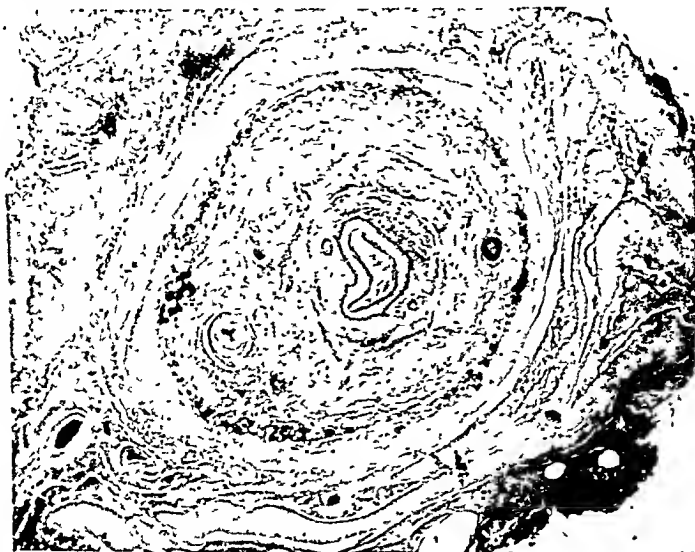


Fig. 6.—Photomicrograph of a cross section of the sinus tract leading from the skin to the spinal cord, with the section taken just proximal to the canal as shown in Fig. 3. The epithelial tract is surrounded by old granulation tissue. About the periphery the dura and arachnoid with psammoma bodies are seen.



Fig. 7.—A higher power photomicrograph of the sinus tissue shown in Fig. 6. The central lumen, which is filled with hair and epithelial debris, is lined by a stratified squamous epithelium. To the right of the central lumen is a sebaceous gland. On the left the line of psammoma bodies is apparent.

*Subsequent examination* four months postoperatively found him walking well, but complaining of an occasional mild pain in the left leg. One-half year later he registered no special complaints except of a mild weakness of the left leg and some tenderness in the scar. Examination four and one-half years postoperatively showed a mild residual paresis of the left leg and trunk, diminished deep sensation in the left leg, and a slight residual diminution of pain and temperature sensation below the fifth dorsal segment. However, the symptoms were minimal, and there was no evidence of recurrence. He has been able to complete his university training and is now actively engaged in his profession.

#### COMMENT

An analysis of this group of cases reveals the fact that pilonidal sinuses occurring over spinal segments higher than the sacrococcygeal region commonly communicate with the central nervous system. Of the 14 cases cited all but 1 were proved at operation. In 12 of these the lesion extended down to or within the meninges, while in the remaining case the lesion was intramedullary. The regional distribution of the sinuses was as follows: cervical, 1; thoracic, 5; lumbar, 3; and sacral, 5. In all but 2 cases there was an associated spina bifida. There was an even distribution as to sex. The ages ranged from 3½ months to 20 years, with only 5 of the patients over 5 years of age.

The signs and symptoms produced by these lesions were primarily neurologic. These were noted in infancy or early childhood in all but 2 of the proved cases, and ranged from a few days up to thirteen years in duration. As a rule the lesions occurring over the lower half of the spine became infected and produced either a subdural abscess or a meningitis. These cases manifested fever, rigidity of the neck and back, and all the other signs characteristic of meningeal irritation. The lesions occurring over the upper half of the spine usually showed no evidence of infection and presented the signs and symptoms typical of a cord tumor. Their common complaint was that of difficulty in walking, due to a spastic paralysis of the lower extremities. Sensory disturbances were usually mild or absent. The correct diagnosis, in the infected as well as the noninfected cases, was made possible only by the recognition of the midline sinus. Surgical removal of the lesion gave excellent results with only 1 mortality in 13 operated cases (7.7 per cent).

It is interesting to note that the patient whose case is herewith presented was apparently free of neurologic symptoms until he developed the measles, and that there was an exacerbation of the symptoms when he contracted chicken pox. These exanthems probably produced an inflammation of the sinus epithelium, increasing the pressure on the cord elements sufficiently to produce a paralysis. The recurrence of progressive symptoms at the time he entered college may be explained on the basis of sex changes incidental to puberty. Hormonal stimulation of hair growth and sebaceous gland activity might well result in an increased pressure within the lesion, sufficient to produce paralysis by pressure on the adjacent cord structures.

*Origin.*—It is generally agreed by research workers that pilonidal sinuses represent a congenital anomaly. However, there exist two main schools of thought as to the true origin of these lesions. The first school was originated by Herrmann and Tourneux<sup>8</sup> and Mallory,<sup>10</sup> and its views are currently being championed by Gage.<sup>5, 6</sup> This group maintains that these lesions are due to an abnormality in the development of the medullary canal, most commonly represented by a failure of obliteration of the same in this (sacrococeygeal) region. The second school, originated by Féré<sup>3</sup> and recently upheld by Fox,<sup>4</sup> maintains that pilonidal sinuses are due to either an infolding of the surface epithelium or a faulty coalescence of the same in early embryonic life.

The case herewith reported apparently presents new and additional evidence to the proponents of the first school. Obviously this case cannot be explained on the basis of a failure of obliteration of the medullary canal. However, the fact that this case, as well as most others reported occurring in the cervical, dorsal, and lumbar regions, showed a communication existing between the skin and the spinal cord or meninges suggests the probability of an incomplete separation of these structures in early embryonic life as the responsible factor. Normally the two medullary folds of the embryo fuse to form a medullary or neural tube, which after four weeks of intrauterine life has become completely separated from the overlying ectodermous covering from which it originated. In the present case the sinus probably communicated directly between the skin surface and the medullary canal which in the adult is represented by the central canal of the cord. This explanation seems all the more probable when the findings of Walker and Buey's second case are considered. In their operative report, discussing work on an abscess lying in the meninges, they state: "The abscess was then opened up to a point where the cavity seemed to continue downward in a hole which appeared to sink into the dorsal surface of the spinal cord." It seems probable that this also communicated with the central canal of the cord.

This explanation for the origin of pilonidal sinuses is also tenable for the more common lesion occurring in the sacrococeygeal region. It must be borne in mind that the medullary canal was also present in this region during the early months of embryonic life, but that these tissues normally undergo atrophy and have usually become obliterated by the time of birth. Only by means of a microscopic study of serial sections of young embryos exhibiting pathology in the sacrococeygeal region can this theory be proved.

#### SUMMARY

1. A review of the literature reveals 13 cases of pilonidal sinuses occurring at spinal segments higher than the sacrococeygeal region. These cases are abstracted, and attention is called to the fact that the symp-

toms are primarily neurologic since these sinuses communicate between the skin and the central nervous system. Spread of infection from the sinus frequently produced signs and symptoms of either a meningitis or a subdural abscess. The noninfected group presented the clinical picture of a cord tumor.

2. A pilonidal sinus occurring over the third dorsal vertebra is described. This case differed from any heretofore recorded in the literature so far as its dilated cystic portion was found at operation to be intramedullary. The signs and symptoms produced by this lesion were typical of a spinal cord tumor.

3. The origin of pilonidal sinuses as a congenital anomaly is discussed. The case herewith reported suggests that these sinuses have their origin in a faulty separation of the medullary or neural canal from the overlying cutaneous epithelium.

I wish to express my sincere appreciation to Dr. Frederick A. Collier and Dr. Max M. Peet, Professors of Surgery, for their cooperation and assistance in this study.

#### REFERENCES

1. Boldrey, E. B., and Elvidge, A. R.: Dermoid Cysts of the Vertebral Canal, *Ann. Surg.* 110: 273-284, 1939.
2. Clark, S. N.: Report of a Case of Spina Bifida Occulta in Cervical Region, *J. Nerv. & Ment. Dis.* 48: 201-205, 1918.
3. Féré, Ch.: Cloisonnement de la cavité pelvienne; utérus et vagin doubles; infundibulum cutané de la région sacrocoecygiennne, *Bull. de la Soc. anat. de Paris* 3: 309, 1878.
4. Fox, S. L.: The Origin of Pilonidal Sinus, *Surg., Gynec. & Obst.* 60: 137, 1935.
5. Gage, M.: Pilonidal Sinus, *Internat. Clin.* 3: 19-32, 1936.
6. Gage, M.: Pilonidal Sinus, *Arch. Surg.* 31: 175, 1935.
7. Hamby, W. B.: Pilonidal Cysts, Spina Bifida Occulta, and Bifid Spinal Cord, *Arch. Path.* 21: 831-838, 1936.
8. Hermann, G., and Tourneux, F.: Les vestiges du segment caudal de la moelle épinière et leur rôle dans la formation de certaines tumeurs sacrocoecygiennes, *Compt. rend. Acad. d. sc., Paris* 104: 1324-1326, 1887.
9. Hipsley, P. L.: Dermoid Cyst of the Spinal Canal, *Australian & New Zealand J. Surg.* 2: 421, 1933.
10. Mallory, F. B.: Sacro-coecygeal Dimples, Sinuses, and Cysts, *Am. J. M. Sc.* 103: 263, 1892.
11. Moise, T. S.: Staphylococcus Meningitis Secondary to a Congenital Sacral Sinus, *Surg., Gynec. & Obst.* 42: 394-397, 1926.
12. Ottonello, P.: Contributo alla conoscenza delle sindromi rare da tumori embriogenetici; dermoide spinale associato a rachischisi; decorso atipico; efficace intervento chirurgico, *Riv. di patol. nerv. & ment.* 41: 512-531, 1933.
13. Ripley, W., and Thompson, D. C.: Pilonidal Sinuses as a Route of Infection in a Case of Staphylococcus Meningitis, *Am. J. Dis. Child.* 36: 785, 1928.
14. Sharpe, W., and Sharpe, N.: Neurosurgery—Principles, Diagnosis & Treatment, Philadelphia, 1928, J. B. Lippincott Co., p. 369.
15. Stammers, F. A.: Spinal Epidural Suppuration With Special Reference to Osteomyelitis of the Vertebrae, *Brit. J. Surg.* 26: 366-374, 1938.
16. Walker, A. E., and Bucy, P. C.: Congenital Dermal Sinuses. A Source of Spinal Meningeal Infection and Subdural Abscesses, *Brain* 57: 401, 1934.

# FUSOSPIROCHETAL ONYCHIA AND PARONYCHIA

TIBOR BENEDEK, M.D., CHICAGO, ILL.

(From the Dermatological Department, Mandel Clinic, Michael Reese Hospital)

ONYCHIA and paronychia caused and sustained by fusospirochetal organisms are extremely rare judged by the scarcity of reports in the literature.

Heller<sup>1</sup> in his most comprehensive monograph on diseases of the nail quoted but two instances from the world literature up to 1927.

I have had the opportunity to observe one case of this condition of about two years' duration. The patient was almost uninterruptedly under medical care, but due to the peculiarity and rarity of the infection, neither were the causative organisms detected nor were efficient therapeutic measures carried out. These circumstances seem to justify the present report.

## REVIEW OF LITERATURE

The oldest report found in the literature deals with observation of Carini<sup>2</sup> on onychia ulcerosa phagedenica. He observed in Brazil an epidemic of ulcerative processes, persistent and painful, localized on the toenails and ending in their destruction. The disease is known in Brazil under the name "*unheiro epidemico*." The microbie flora of the ulcers consists in *Bacillus fusiformis* plus *Spirochaeta plaut-vincenti*. The victims of the infection are mainly peasants walking barefooted on the humid infested soil. Iodoform seemed to be effective against the fusospirochetal infection.

Aars Nicolaysen<sup>3</sup> observed two cases of fusospirochetal onychia. He also emphasizes the extreme rarity of this type of infection. He could not find any reference to this infection either in the great textbooks of surgery or in Klapp's monograph on paronychia. Prior to his observation, there were no publications on the subject in the whole Scandinavian medical literature.

His first case concerned a 62-year-old dentist with a swollen right index finger. The patient stated that a few days previously he had probably pricked his finger with an injection needle just used for the anesthesia at the extraction of a carious tooth. Within a few days the finger had grown worse and a wide incision made on the flexor side of the middle phalange showed the tissue to be grayish, discolored, and imbued with a thin, serous pus of a certain loathsome, foul smell. The tendon sheath seemed not to be affected, but the process was still progressing. Along the flexor and extensor side of the finger, incision showed the tissue comprising the flexor tendon and the basal phalangeal

bone to be to a great extent necrotic. There were no signs of either lymphangitis or ascending tendovaginitis. Bacteriologic examination revealed fusospirochetal flora. Three injections of neosalvarsan (0.3, 0.45, 0.6 Gm.) brought about complete healing.

The second case related to a housewife, 54 years of age, whose right index finger had been severely bitten by her husband in an epileptic fit when she tried to keep his tongue clear of his teeth. The finger very soon started aching, growing steadily worse. The distal phalange of the right index finger was very tender and swollen, but in a rather diffuse manner without any firm infiltration or formation of abscess. From the two small wounds a blood-tinged serous fluid was discharged. The whole finger showed a diffuse edematous swelling, without any signs of either lymphangitis or tendovaginitis. Intravenous injections of neosalvarsan brought about healing.

Carone<sup>4</sup> reported the case of a 9-year-old girl who, about six months before she was seen, had had a splinter of wood under the fingernail of the right thumb removed by her mother by means of a nail. From that moment she suffered from a suppurative condition starting in the bed of the nail, spreading little by little to the distal phalange in spite of the surgical removal of the nail. The thumb, however, became swollen, the pain was violent, temperature went up to 38 to 39° C., and the distal phalange was exarticulated. This procedure, however, did not stop the progress of infection. The proximal phalange became swollen to twice its normal size and the skin around it was purple. Pressure elicited violent pain. X-ray showed the necrosis of the first phalange of the thumb. The first bacteriologic examination, six months after the condition started, of the fibrous exudate revealed a pure flora of fusospirochetal organisms.

Local application of arsphenamine did not change the clinical picture and in order to stop the progress metacarpophalangeal exarticulation was performed with multiple incisions in the surrounding soft tissues, which led to total cure.

Biopsy of different pieces of tissue removed at different points from the affected thumb showed a thick layer of necrotic and necrobiotic tissue, disintegrating cells embedded in a fibrin network, and a deep layer of tissue in the state of inflammation revealing a histiocytic reaction. There were no other characteristic signs.

#### CASE REPORT

A white boy, 17 years old, affected with hereditary dystrophy of the nails and hair,\* came to the dispensary in March, 1938, suffering from onychia and paronychia of several fingers of about two years' duration. Since the start of the affection, he has always been under medical care; several times he has changed physicians and the curative measures applied have been changed without any success.

<sup>4</sup> The hereditary dystrophy of the hair and nails was reported in *J. Invest. Dermat.* 4: 285-293, 1941.

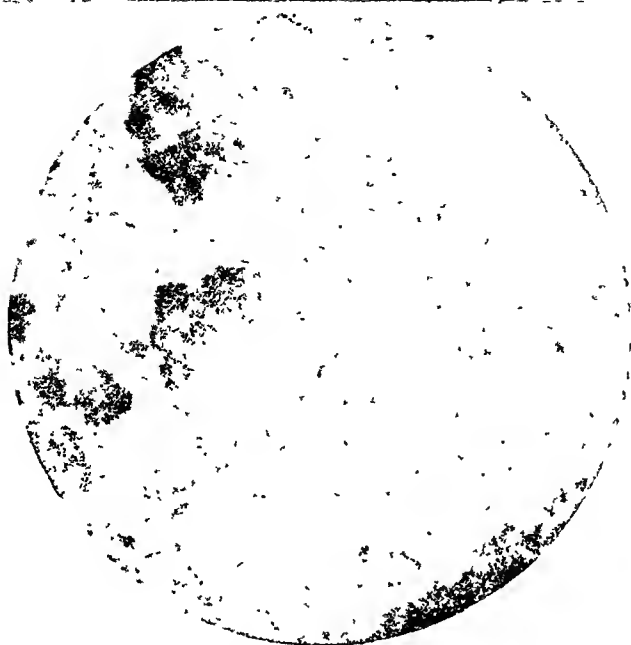


Fig. 1.—Smear from the thin fetid pus from underneath the affected nail. Gram stain. Photomicrograph, 1,500 diameters.



Fig. 2.—Section from the posterior nail wall of the right thumb. Hematoxylin-eosin stain. Photomicrograph, 500 diameters.



bone to be to a great extent necrotic. There were no signs of either lymphangitis or ascending tendovaginitis. Bacteriologic examination revealed fusospirochetal flora. Three injections of neosalvarsan (0.3, 0.45, 0.6 Gm.) brought about complete healing.

The second case related to a housewife, 54 years of age, whose right index finger had been severely bitten by her husband in an epileptic fit when she tried to keep his tongue clear of his teeth. The finger very soon started aching, growing steadily worse. The distal phalange of the right index finger was very tender and swollen, but in a rather diffuse manner without any firm infiltration or formation of abscess. From the two small wounds a blood-tinged serous fluid was discharged. The whole finger showed a diffuse edematous swelling, without any signs of either lymphangitis or tendovaginitis. Intravenous injections of neosalvarsan brought about healing.

Carone<sup>4</sup> reported the case of a 9-year-old girl who, about six months before she was seen, had had a splinter of wood under the fingernail of the right thumb removed by her mother by means of a nail. From that moment she suffered from a suppurative condition starting in the bed of the nail, spreading little by little to the distal phalange in spite of the surgical removal of the nail. The thumb, however, became swollen, the pain was violent, temperature went up to 38 to 39° C., and the distal phalange was exarticulated. This procedure, however, did not stop the progress of infection. The proximal phalange became swollen to twice its normal size and the skin around it was purple. Pressure elicited violent pain. X-ray showed the necrosis of the first phalange of the thumb. The first bacteriologic examination, six months after the condition started, of the fibrous exudate revealed a pure flora of fusospirochetal organisms.

Local application of arsphenamine did not change the clinical picture and in order to stop the progress metacarpophalangeal exarticulation was performed with multiple incisions in the surrounding soft tissues, which led to total cure.

Biopsy of different pieces of tissue removed at different points from the affected thumb showed a thick layer of necrotic and necrobiotic tissue, disintegrating cells embedded in a fibrin network, and a deep layer of tissue in the state of inflammation revealing a histiocytic reaction. There were no other characteristic signs.

#### CASE REPORT

A white boy, 17 years old, affected with hereditary dystrophy of the nails and hair,\* came to the dispensary in March, 1938, suffering from onychia and paronychia of several fingers of about two years' duration. Since the start of the affection, he has always been under medical care; several times he has changed physicians and the curative measures applied have been changed without any success.

\*The hereditary dystrophy of the hair and nails was reported in *J. Invest. Dermat.* 4: 285-293, 1941.

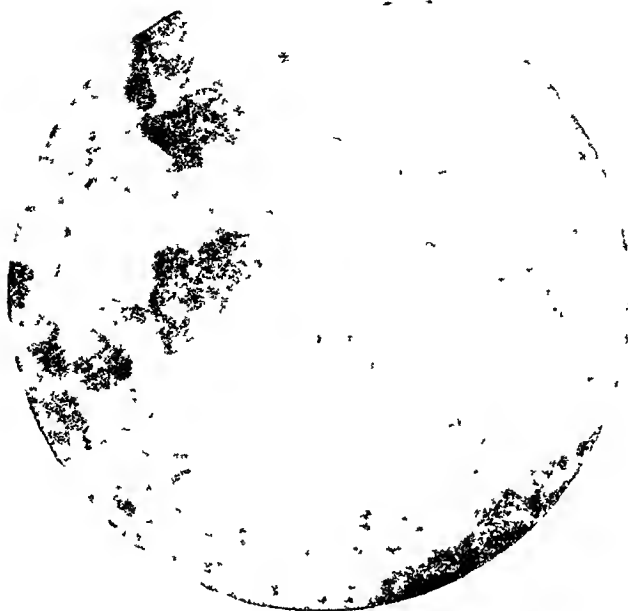


Fig 1—Smear from the thin fetid pus from underneath the affected nail Gram stain Photomicrograph, 1,500 diameters

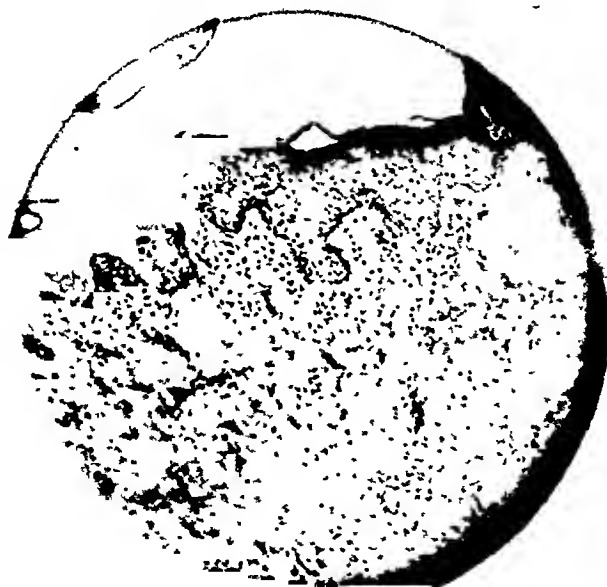


Fig 2—Section from the posterior nail wall of the right thumb Hematoxylin-eosin stain Photomicrograph, 500 diameters

On admission the left hand showed onychia and paronychia on the third and fourth fingers, and on the right hand the first, third, and fourth fingers were affected.

The aspect of the affected fingers was the same. The nail wall was red, hot, swollen all around, and the redness was clearly marked toward the normal skin. The reddened area measured 5 mm. in breadth. The nail was loosened and stuck only under the posterior nail wall. The nail bed was deep red, covered with a thin grayish green, terrible fetid, pus of nauseating odor. The nail phalanges of the affected fingers were extremely tender.

The smell was so unbearable that he wore thick bandages on the affected fingers to lessen the odor, but these did only little good. If he took off the bandage, the smell in a few minutes was so bad in the consultation room that the window had to be opened.

Smears from the discharges of the affected nails showed pure culture of fusospirochetal organisms.

Further laboratory examinations showed: Wassermann and Kahn tests, negative; blood: hemoglobin, 70 per cent (Sahli); red cells, 4,100,000; white cells, 5,800; neutrophil polymorphonuclear leucocytes, 48 per cent; lymphocytes, 52 per cent; urine: normal, acid, specific weight 1.026; basal metabolic rate: satisfactory, variation plus 3.1 per cent.

X-ray revealed no changes in the distal phalanges of the affected fingers.

The nail wall of the right thumb was removed for histologic examination.

The section showed perfectly hyperkeratosis of the stratum corneum. Stratum granulosum was present throughout the whole section. The rete malpighii did not show acanthosis, but there was a moderate spongiosis throughout the whole section with the scattered infiltration of a few wandering cells. The lymph spaces and vessels, in the papillary portion of the corium, were somewhat dilated and surrounded with a moderate perivascular infiltration. The dilation of the vessels and lymph spaces of the deeper corium was more pronounced and there was also a somewhat denser perivascular infiltration consisting of small lymphocytes. Throughout the whole corium the connective tissue was edematous. No microorganisms of any description could be detected in the sections.

Concerning therapy, a 1 per cent aqueous solution of neoarsphenamine was tried as local application under the nail bed, without success. Afterward he was given three injections of neoarsphenamine, 0.3 Gm. intravenously every fourth day, without any result. Finally the nails of all the affected fingers were surgically removed and under antiseptic treatment cure was attained.

#### COMMENTS

The extreme rarity of fusospirochetal onychia and paronychia makes it understandable that nobody thought of this possibility in the course of this most annoying affliction of two years' duration.

Hindasek<sup>5</sup> could not find among 6,000 cases of different, mostly severe paronychia during seven years a single case of fusospirochetal infection. Likewise, not a single case report could be found by painstaking search in the American literature. The present case thus seems to be the first report on fusospirochetal infection of the nail.

The total neglect of bacterioscopic examination of the peculiar thin fetid pus, of course, cannot be excused by the rarity of the condition.

Benedek, Zakon, and Harris<sup>6</sup> emphasized the absolute necessity of bacterioscopic examination in their observation of a likewise rare affliction of fusospirochetal osteomyelitis of the jaw. The present case is

again a warning not to neglect the bacterioscopic examination in every instance; in this case it would have saved two years' misery in the patient's life and spared the extreme annoyance for his family.

Among the few cases reported, Aars Nicolaysen's two observations have a special interest for us on account of the similar mechanism of the infection in my patient.

His first patient, a dentist, pricked his finger with an injection needle used in anesthesia of a carious tooth. His second patient was severely bitten by her husband in aiding him in an epileptic seizure.

In Carone's and Carini's cases injury was similarly an important element, but human saliva did not come in contact with the injured tissues at all.

From the description of his parents, my patient must have had a pompholyx of the nail bed anterior to the fusospirochetal infection of the nails. Moreover, he had the bad habit of gnawing on the dwarf nails.

In smears the oral cavity of this patient (tonsils, gums) revealed, at repeated instances, the presence of pure culture of fusospirochetal organisms, without the least sign of a fusospirochetal process on the oral mucosa.

With a high degree of probability it can be assumed that the patient having already a pathologic process in the nail bed (pompholyx) and having the habit of gnawing the nails, infected the nail bed with fusospirochetal organisms of his own oral cavity.

Fusospirochetal organisms do not start an infection primarily in healthy normal tissues. They easily invade, however, bruised, injured tissues causing and sustaining for a long time a more or less dangerous, slowly progressing infection.

At the first sight of my patient I had the impression that some extraordinary, unusual cause might play a decisive role in the onychia and paronychia. The long duration of the infection with surprisingly slow progress; the relatively moderate pain, at least in the beginning of the infection; the diffuse, edematous state of the nail phalanges without distinct localization of an evident center of suppuration; the total lack of lymphangitis and lymphadenitis; and last but not least, the thin grayish pus with the extreme fetid nauseating smell were the distinct features differentiating this type of infection from infections with common pus bacteria.

In Aars Nicolaysen's cases intravenous injections of arsphenamine had a prompt curative effect. In my case they totally failed.

In my judgment the best and most successful way of treating fusospirochetal infection (onychia, paronychia, osteomyelitis) is the surgical procedure of removing the anaerobic conditions (bruised, injured, or otherwise impaired tissues), the only adequate cultural conditions for the existence of these organisms.

## SUMMARY

Onychia and paronychia caused and sustained by fusospirochetal organisms in a white boy, aged 17 years, are described, seemingly the first such observation in the American literature.

The condition lasted for two years with slow but definite progress, without lymphangitis or lymphadenitis.

Local application and intravenous administration of neoarsphenamine were without success.

Surgical removal of the nails of the affected fingers brought about prompt healing.

The necessity of prompt bacterioscopic examination of the discharge is urgently advocated in every case of this disease.

## REFERENCES

1. Heller, J.: Die Krankheiten der Nägel. Jadassohn's Handbuch der Haut- u. Geschlechtskr. J. Springer, Berlin 13: 2, 1927.
2. Carini, M.: Onyxis ulcreux phagedenique, Presse med. p. 30, 1916.
3. Aars Nicolaysen, N.: Two Panaritia With Unusual Infection, Acta chir. Scandinav. 76: 361-367, 1935.
4. Carone, C.: Su di una rara complicanza di paterccio osseo, Riv. di chir. 2: 242-48, 1936.
5. Hudacsek, E.: Beiträge zur Kenntnis der Knochen und Gelenkpanaritien und Sehnencheidenphlegmonen, Bruns' Beitr. z. klin. Chir. 161: 264-272, 1935.
6. Benedek, T., Zakon, S. J., and Harris, J. T.: Osteomyelitis of the Lower Jaw Caused and Maintained by Fusospirochetal Infection, Illinois M. J. 75: 347-351, 1939.

# MALIGNANT MENINGIOMAS

## A CLINICAL AND PATHOLOGIC STUDY

OSCAR A. TURNER, M.D., WINCHELL MCK. CRAIG, M.D., AND  
JAMES W. KERNOHAN, M.D., ROCHESTER, MINN.

*(From the Mayo Foundation and the Sections on Neurologic Surgery and on  
Pathologic Anatomy and Surgical Pathology, the Mayo Clinic)*

DESPITE the voluminous literature concerning the meningeal tumors, little attention has been given to the malignant capacity which certain of these tumors exhibit, nor has there been any detailed consideration of those growths which microscopically have many of the characteristics common to the malignant tumors arising elsewhere in the body. Although a sarcomatous type of meningioma was included in the classification by Bailey and Bucy,<sup>1</sup> it has been infrequently reported and these authors stated that it is rarely encountered. Thus, Cushing and Eisenhardt<sup>2</sup> in their recent monograph found that but 6, or 1.9 per cent, of 313 meningeal tumors could be considered as malignant, and Baker<sup>3</sup> encountered 1 sarcomatous meningioma, or 1.1 per cent, in his series of 88 tumors. Globus,<sup>4</sup> however, expressed the opinion that sarcomatous meningiomas are not as rare as Bailey suggested and attributed the small percentage in published statistics to the fact that they are not fully recognized. Evidence to substantiate this can be found in the early report of Craig,<sup>5</sup> who encountered 11 examples, or 19.3 per cent, after a review of 57 cases at the Mayo Clinic. Penfield and his co-workers,<sup>6</sup> in a study of intracranial tumors and symptomatic epilepsy, noted the presence of 5 malignant meningeal tumors, sarcomas and fibrosarcomas, or 7 per cent, among 71 examples. Reports of large series of intracranial meningeal tumors are not frequently published, but from those available it can be noted that the percentage of malignant meningeal tumors varies considerably. In several of the reports, such as that of Frazier and Alpers,<sup>7</sup> no mention of the malignant variety is made.

In the present study, 370 intracranial meningeal tumors seen at the Mayo Clinic were examined microscopically. Of this group, 36 were selected on the basis of the microscopic examination as showing definite malignant characteristics. With but few exceptions the 370 tumors were operative specimens and in some cases both surgical and necropsy material was available for study. Certain limitations were made concerning those malignant tumors selected for study in that only those were chosen which were formed growths and which could be classed under the broad heading of meningioma as it conforms to the conception

among neurosurgeons and neuropathologists. Thus, 5 cases of perithelial sarcoma of the cerebellum, such as were described by Bailey,<sup>8</sup> were not included. A single example of a highly malignant cerebellar sarcoma of the Ewing type, probably vascular in origin, as well as a case of oat-cell neoplasm, was also excluded. The latter was possibly metastatic from the lung although this was not evident clinically. One very unusual osteogenic sarcoma of meningeal origin encountered in the series has been the subject of a separate report.<sup>9</sup>

Of the 36 growths selected for study, 22 occurred in men and 14 in women. As is to be expected, the majority, 22 in number, occurred in the third, fourth, and fifth decades with the extremes at the ages of 8 and 60 years.

#### CLASSIFICATION

Because of the variable degree of malignancy exhibited in the microscopic appearance of the different tumors and the different morphologic characteristics, it is necessary to attempt some grouping as a basis for study and classification. The classification was derived essentially from the microscopic appearance of the tumors studied, and although the basic feature was the grading of the degree of malignancy, some attempt was made also to identify the major structural elements of the tumors. It is recognized that any such classification, in a large sense, must be arbitrary and that no sharp line of demarcation exists between the different components.

In meningeal tumors of early or low-grade malignancy, the malignancy, in general, is reflected in the tissue architecture rather than in the cell type. These tumors are highly cellular and vascular, usually with little variation in cell and nuclear size and structure. Little evidence of psammoma formation is present. Whorls, if present at all, are not prominent, and usually a definite pattern to the tissue is lacking. Mitotic figures are present in moderate numbers. Giant cells, if present, are in early forms.

In meningeal tumors with advanced or well-marked malignancy, the malignant character of the tumor is reflected in the cell type and structure as well as in the general tissue architecture.

A. Tumors of meningothelial or related type with malignancy evident in the parenchyma, as contrasted with the following subgroup, are cellular tumors with little or no whorl or psammoma formation. Mitotic figures are abundant and giant cells are frequently encountered in many of the tumors. There is considerable variation in size and type of cells. The tumor is quite vascular. The stroma is well demarcated from the parenchyma and may be scanty. There may be invasion of dura, brain, bone and often of the stroma of the tumor itself. Many of these growths are composed of large epithelioid cells.

B. In the sarcoma-like form, manifest in the fibroblastic variety of tumor or derived from the stromal elements of other forms, there may

be the characteristic streaming, interlacing pattern of a fibroblastic tumor, or the pattern of the tissue may be quite irregular and broken. In the latter instance, giant cells and bizarre forms may be encountered. Mitotic figures are present, usually in large numbers.

Malignant tumors of variable activity, possibly arising from the dura itself, are related to the foregoing group but take on certain of the characteristics of other forms; that is, the fibromyxosarcoma, fibrochondrosarcoma or osteogenic meningeal sarcoma. These are highly malignant, atypical growths which have an unusual and bizarre microscopic appearance with numerous giant cell forms and other atypical cells, and probably are atypical stromal tumors related to the sarcomatous form.

As can be seen, no attempt has been made to include in the classification the perithelial tumors (peritheliomas and perithelial sarcomas) described by Bailey and by Hsü,<sup>10</sup> the diffuse or formed melanoepitheliomas,<sup>11, 12</sup> or the reticulum-cell sarcoma described by Yuile<sup>13</sup> which is probably related to the perithelial sarcoma if not identical with it. The so-called primary fibroblastoma of the brain, examples of which have been described by Mallory<sup>14</sup> and by Cottrell,<sup>15</sup> is considered to fall in the group of sarcomatous meningeal tumors. The apparently intracerebral situation of some of these can be explained upon a leptomeningeal origin deep within a sulcus. No mention has been made of the clinical aspect of the various groups; this will be considered along with the individual tumor types.

#### MENINGEAL TUMORS OF LOW-GRADE MALIGNANCY

The consideration of these tumors of low-grade malignancy but, nevertheless, of vigorous growth is a necessary preliminary to the consideration of those which exhibit advanced malignant characteristics. As has been stated, it is this group of meningeal tumors that has received the least attention, for whatever consideration has been given to the malignant meningeal tumors has been directed to those which are obviously sarcomatous and, in most instances, highly malignant. Twenty-two tumors were studied in this group and among these were all the variations of structure encountered in the meningeal tumors. Although within the group there were variations in the degree of activity, the grading of these meningeal tumors cannot be carried too far. Certain common characteristics of cell structure and tissue architecture were present and will be considered.

The 22 tumors were equally distributed between male and female patients with age extremes of 12 and 57 years. All but 2 of the tumors occurred in the third to the fifth decades. More than one-half of the tumors were removed from the frontal or frontoparietal region, and others were distributed over the remainder of the brain. One growth occurred in the cerebellopontine angle and one, apparently originating in the torcular region, involved both sides of the tentorium. Of the size and extent of the tumors, more information will be given later.



among neurosurgeons and neuropathologists. Thus, 5 cases of perithelial sarcoma of the cerebellum, such as were described by Bailey,<sup>8</sup> were not included. A single example of a highly malignant cerebellar sarcoma of the Ewing type, probably vascular in origin, as well as a case of oat-cell neoplasm, was also excluded. The latter was possibly metastatic from the lung although this was not evident clinically. One very unusual osteogenic sarcoma of meningeal origin encountered in the series has been the subject of a separate report.<sup>9</sup>

Of the 36 growths selected for study, 22 occurred in men and 14 in women. As is to be expected, the majority, 22 in number, occurred in the third, fourth, and fifth decades with the extremes at the ages of 8 and 60 years.

#### CLASSIFICATION

Because of the variable degree of malignancy exhibited in the microscopic appearance of the different tumors and the different morphologic characteristics, it is necessary to attempt some grouping as a basis for study and classification. The classification was derived essentially from the microscopic appearance of the tumors studied, and although the basic feature was the grading of the degree of malignancy, some attempt was made also to identify the major structural elements of the tumors. It is recognized that any such classification, in a large sense, must be arbitrary and that no sharp line of demarcation exists between the different components.

In meningeal tumors of early or low-grade malignancy, the malignancy, in general, is reflected in the tissue architecture rather than in the cell type. These tumors are highly cellular and vascular, usually with little variation in cell and nuclear size and structure. Little evidence of psammoma formation is present. Whorls, if present at all, are not prominent, and usually a definite pattern to the tissue is lacking. Mitotic figures are present in moderate numbers. Giant cells, if present, are in early forms.

In meningeal tumors with advanced or well-marked malignancy, the malignant character of the tumor is reflected in the cell type and structure as well as in the general tissue architecture.

A. Tumors of meningothelial or related type with malignancy evident in the parenchyma, as contrasted with the following subgroup, are cellular tumors with little or no whorl or psammoma formation. Mitotic figures are abundant and giant cells are frequently encountered in many of the tumors. There is considerable variation in size and type of cells. The tumor is quite vascular. The stroma is well demarcated from the parenchyma and may be scanty. There may be invasion of dura, brain, bone and often of the stroma of the tumor itself. Many of these growths are composed of large epithelioid cells.

B. In the sarcoma-like form, manifest in the fibroblastic variety of tumor or derived from the stromal elements of other forms, there may

be the characteristic streaming, interlacing pattern of a fibroblastic tumor, or the pattern of the tissue may be quite irregular and broken. In the latter instance, giant cells and bizarre forms may be encountered. Mitotic figures are present, usually in large numbers.

Malignant tumors of variable activity, possibly arising from the dura itself, are related to the foregoing group but take on certain of the characteristics of other forms; that is, the fibromyxosarcoma, fibrochondrosarcoma or osteogenic meningeal sarcoma. These are highly malignant, atypical growths which have an unusual and bizarre microscopic appearance with numerous giant cell forms and other atypical cells, and probably are atypical stromal tumors related to the sarcomatous form.

As can be seen, no attempt has been made to include in the classification the perithelial tumors (peritheliomas and perithelial sarcomas) described by Bailey and by Hsü,<sup>10</sup> the diffuse or formed melanoepitheliomas,<sup>11, 12</sup> or the reticulum-cell sarcoma described by Yuile<sup>13</sup> which is probably related to the perithelial sarcoma if not identical with it. The so-called primary fibroblastoma of the brain, examples of which have been described by Mallory<sup>14</sup> and by Cottrell,<sup>15</sup> is considered to fall in the group of sarcomatous meningeal tumors. The apparently intracerebral situation of some of these can be explained upon a leptomeningeal origin deep within a sulcus. No mention has been made of the clinical aspect of the various groups; this will be considered along with the individual tumor types.

#### MENINGEAL TUMORS OF LOW-GRADE MALIGNANCY

The consideration of these tumors of low-grade malignancy but, nevertheless, of vigorous growth is a necessary preliminary to the consideration of those which exhibit advanced malignant characteristics. As has been stated, it is this group of meningeal tumors that has received the least attention, for whatever consideration has been given to the malignant meningeal tumors has been directed to those which are obviously sarcomatous and, in most instances, highly malignant. Twenty-two tumors were studied in this group and among these were all the variations of structure encountered in the meningeal tumors. Although within the group there were variations in the degree of activity, the grading of these meningeal tumors cannot be carried too far. Certain common characteristics of cell structure and tissue architecture were present and will be considered.

The 22 tumors were equally distributed between male and female patients with age extremes of 12 and 57 years. All but 2 of the tumors occurred in the third to the fifth decades. More than one-half of the tumors were removed from the frontal or frontoparietal region, and others were distributed over the remainder of the brain. One growth occurred in the cerebellopontine angle and one, apparently originating in the tentorial region, involved both sides of the tentorium. Of the size and extent of the tumors, more information will be given later.

There was considerable variation in the duration of symptoms as figured to the time of the first admission to the hospital. In 12 of the 22 cases, symptoms of one sort or another had been present for one year or less. The longest history was six years in the case of tumor of the sphenoid ridge in a 47-year-old woman. At operation this tumor was found to have extended widely throughout the anterior cranial fossa, and despite a grossly complete removal, the patient died seven months after operation with symptoms suggestive of recurrence of the tumor. In one instance there was a five-year history and at operation a subtotal removal of a tumor of the tuberculum sellae was carried out. Death followed from postoperative complications and at necropsy the tumor was found to have extended superiorly sufficiently to compress the left lateral ventricle and third ventricle and to have invaded the sella turcica. In 7 of the 22 cases there were histories varying from three to six years in duration and for these 7 the average duration of symptoms was just more than four years. In the remaining 15 cases, the duration of symptoms was two years or less and the average for these was between eleven months and one year. The average duration of symptoms for the entire group was two years and three months.

The duration of symptoms alone is a poor index of the rapidity of growth of a tumor, and it is obvious that tumors situated over relatively silent portions of the hemisphere will attain large size and even extend widely before making known their presence. As an example, one patient having a three-year history was found to have a large frontoparietal tumor which had penetrated the calvarium and extended widely beneath the scalp. Similarly, one growth originating apparently from the torcular region was found to measure 10 cm. in width at the time of operation and had caused erosion and multiple regions of destruction in the occipital bone. It had invaded the tentorium and presented on either side of it. One meningeal tumor was found in the cerebellopontine angle in a patient having a history of two years' duration. At operation it was found to have invaded and penetrated the tentorium, causing compression of the supratentorial structures as well as extending between the pons and the cerebellum and between the cranial nerves.

Involvement of the bone was present in 8 instances. In 2 cases definite invasion and penetration had occurred and erosion and destruction of bone were noted in the torcular tumor described previously. In 4 instances, in all of which there were histories of ten months' duration or less, hyperostosis with increased vascularity was evident.

In this group evidence of recurrence of the tumor occurred in 8 instances in which there was an average duration of seven and one-half months between the time of operation and the first symptom. In one instance in which symptoms had been present for nine months prior to operation, a second operation five months later disclosed a recurrent tumor as large as that removed at the first operation. One month later

all the former signs of recurrence of the tumor were again present. The necessity of care in the interpretation of figures for recurrence may be shown by the case of a 12-year-old girl who had evidence of an intracranial tumor for six months prior to the removal of a large intracerebral growth. Despite undoubted clinical evidence of recurrence five months after operation, death did not occur until two and one-half years later.

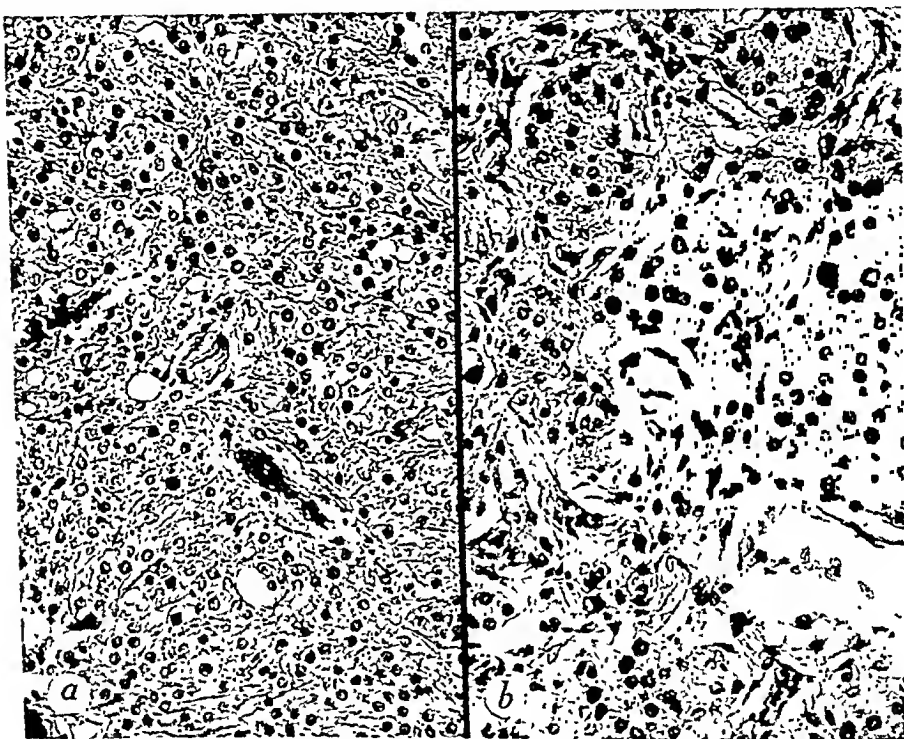


Fig. 1.—Tumors of low-grade or early malignancy. *a*, Note the epithelioid type of cell with well-defined cytoplasmic outlines, the cellularity of the tissue, and the absence of variation in cell size (hematoxylin and eosin  $\times 200$ ). *b*, Note the chromophilic nuclei and moderate variation in the size of the cells. This tumor contained many giant cells and mitotic figures (hematoxylin and eosin  $\times 220$ ).

*Pathology.*—No attempt will be made to divide the tumors of this group further upon the basis of differences in tumor activity. However, for the purposes of description several morphologic groups have been separated. Certain characteristics are common to all these meningeal tumors of low-grade malignancy and will be considered first. A characteristic feature of almost every tumor in this group was the marked cellularity of the tissue (Fig. 1*a*). Associated was a high degree of vascularity, almost all of the vessels being well formed but thin and related to the stromal elements. The latter varied in different tumors and in some showed unusual overgrowth such as is often seen in certain of the gliomas. The number of mitotic figures seen in the different

There was considerable variation in the duration of symptoms as figured to the time of the first admission to the hospital. In 12 of the 22 cases, symptoms of one sort or another had been present for one year or less. The longest history was six years in the case of tumor of the sphenoid ridge in a 47-year-old woman. At operation this tumor was found to have extended widely throughout the anterior cranial fossa, and despite a grossly complete removal, the patient died seven months after operation with symptoms suggestive of recurrence of the tumor. In one instance there was a five-year history and at operation a subtotal removal of a tumor of the tuberculum sellae was carried out. Death followed from postoperative complications and at necropsy the tumor was found to have extended superiorly sufficiently to compress the left lateral ventricle and third ventricle and to have invaded the sella turcica. In 7 of the 22 cases there were histories varying from three to six years in duration and for these 7 the average duration of symptoms was just more than four years. In the remaining 15 cases, the duration of symptoms was two years or less and the average for these was between eleven months and one year. The average duration of symptoms for the entire group was two years and three months.

The duration of symptoms alone is a poor index of the rapidity of growth of a tumor, and it is obvious that tumors situated over relatively silent portions of the hemisphere will attain large size and even extend widely before making known their presence. As an example, one patient having a three-year history was found to have a large frontoparietal tumor which had penetrated the calvarium and extended widely beneath the scalp. Similarly, one growth originating apparently from the torcular region was found to measure 10 cm. in width at the time of operation and had caused erosion and multiple regions of destruction in the occipital bone. It had invaded the tentorium and presented on either side of it. One meningeal tumor was found in the cerebellopontine angle in a patient having a history of two years' duration. At operation it was found to have invaded and penetrated the tentorium, causing compression of the supratentorial structures as well as extending between the pons and the cerebellum and between the cranial nerves.

Involvement of the bone was present in 8 instances. In 2 cases definite invasion and penetration had occurred and erosion and destruction of bone were noted in the torcular tumor described previously. In 4 instances, in all of which there were histories of ten months' duration or less, hyperostosis with increased vascularity was evident.

In this group evidence of recurrence of the tumor occurred in 8 instances in which there was an average duration of seven and one-half months between the time of operation and the first symptom. In one instance in which symptoms had been present for nine months prior to operation, a second operation five months later disclosed a recurrent tumor as large as that removed at the first operation. One month later

the meningotheial variety and all were quite cellular and highly vascularized. An occasional one appeared to be almost hemangiomatous owing to the frequency with which small but well-formed vessels were encountered. Whorl formation was not marked in any, but in several the tissue showed well-formed lobules due to the manner in which the stroma was disposed. Mitotic figures were present in all the group, but in none were they abundant. Giant cell forms were not seen.

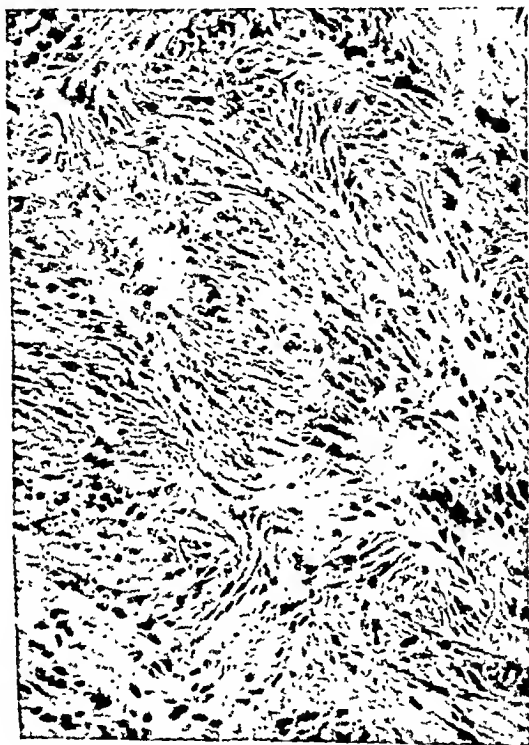


Fig. 2.—Highly cellular tumor of low-grade malignancy and of stromal origin (hematoxylin and eosin  $\times 180$ .)

#### MENINGEAL TUMORS OF PRONOUNCED MALIGNANCY

In this second group of meningeal tumors in which the malignant character was more pronounced, the change was evident microscopically both in the cell structure and in the architectural arrangement of the tumor tissue. There were 14 tumors in this group and they will be considered together for clinical purposes.

Of the 14 tumors, 11 were in male patients. The age distribution was not unusual with the exception of an 8-year-old child from whom a large frontoparietal growth was removed. It is of interest that in this same family another child had died at the age of 5 years with the symptoms of stiffness of the legs, tremor, and headache, a diagnosis of *gumma cerebri* having been made by the family physician.

tumors varied but in none were they abundant. The architecture varied somewhat with the morphologic character of the tissue. In the fibroblastic tumors considerable streaming and some tendency toward whorl formation about the vessels were seen, but discrete whorls and psammoma formation were present to any marked degree in only one growth. Lobulation of the tissue was present in several of the growths, particularly when the connective tissue was prominent and the tumor was of the meningothelial variety. Giant cells, as such, were rarely seen, although in several of the tumors early forms were evident. The cell structure varied with the tumor type, but in general there was little variation in the size of the cells or of the nuclei. Calcification was rarely seen and, when present consisted of a few scattered deposits.

In this group there were four tumors in which the parenchyma was composed of columns and cords of large epithelioid cells. These corresponded closely to the Type V of Cushing and Eisenhardt, three being similar to their Variant 1 and one to their Variant 2. The individual cells were large and cuboidal or polygonal with abundant finely granular cytoplasm and large chromophilic nuclei (Fig. 1b). In several of the growths there were scattered regions in which the cells appeared round or fusiform. In one tumor there was considerable variation in the size of both nuclei and cells, and large and often atypical nuclear forms were encountered frequently. All the tumors were well vascularized and contained a moderate amount of connective tissue distributed in strands between the cell groups. No reticulum or collagen formation was noted. There was no marked perivascular arrangement, and only in one of the growths was there a suggestion of whorl formation. All the tumors contained a moderate number of mitotic figures.

The malignant appearance of these tumors has been commented upon by Cushing and Eisenhardt, who stated that sarcomatous-like regions were encountered in several of their 18 examples. In general, these four growths represent the most active of the group of low-grade malignant meningiomas. Peculiarly enough, the duration of symptoms prior to operation in the 4 cases ranged from six months to six years.

In the group of low-grade malignant meningiomas, the differentiation between those of parenchymatous and those of stromal origin is frequently difficult and often the morphologic character of the tumor is not clear. In the group there were 4 tumors considered to be of connective tissue origin. In only 1 was the fibroblastic character highly developed (Fig. 2), and in this tumor early giant cell forms could be identified. All the tumors showed some tendency toward streaming, but with the exception of that noted previously, this was not marked. Mitotic figures were not abundant and several tumors appeared to consist of a mixture of meningothelial and fibroblastic elements.

There were marked differences in the tissue architecture and cell type in the remaining 14 tumors. In general, all appeared to be related to

and the brain. The tumor was composed of sheets of large cells with hyperchromatic nuclei of varying size. In some regions the tissue appeared epithelioid and elsewhere meningotheliomatous. Giant cells were plentiful and mitotic figures moderate in number. The tissue architecture was irregular with no whorls. The tumor was highly vascular, but there were extensive regions of degeneration.

CASE 2.—A large, frontal, parasagittal tumor occurred in a 57-year-old man who had a three-year history complicated by several episodes of local trauma. Microscopically, the tumor appeared well encapsulated and composed of cords and columns of polygonal cells, similar in many respects to those of the epithelioid variety (Fig. 3a). The nuclei were hyperchromatic and showed considerable variation in size and shape, and occasional giant cells were observed. There were a moderate number of mitotic figures. The cell columns were separated by vascularized strands of connective tissue which were invaded by the tumor parenchyma (Fig. 3b).

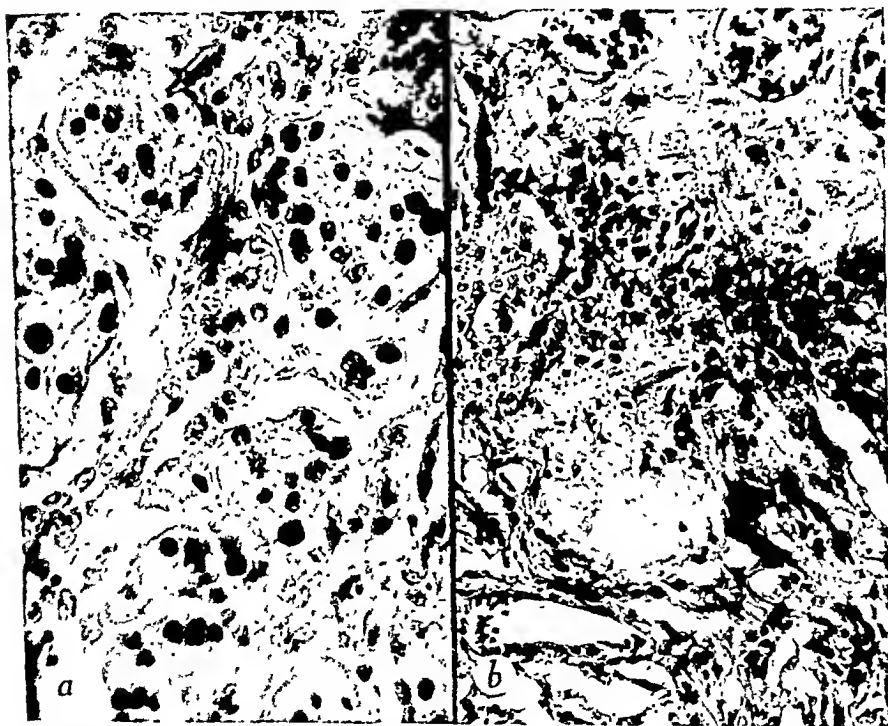


Fig. 3—Case 2. Highly malignant tumor of parenchymatous origin. *a*, High magnification to show the character of the individual cells. Note the marked variation in the size of the nuclei and the mitotic figures. Tumor of epithelioid type (hematoxylin and eosin  $\times 300$ ). *b*, To show invasion of the supporting stroma by tumor cells. There has been invasion of a band of hyalinized connective tissue about several vessels (hematoxylin and eosin  $\times 205$ ).

CASE 3.—A large occipitoparietal growth was removed from a 36 year old man who had had symptoms for nine months prior to operation. Objective signs of recurrence were present seven years after operation, and at the time of the second operation, five years later, the tumor had invaded and perforated the calvarium and there was involvement of the falx, the longitudinal sinus, and the tentorium. Microscopically, the tumor was composed of nests, small whorls, and columns of cells separated by edema and hyalinized connective tissue (Fig. 4a). The tissue architecture was quite disorganized. The tumor cells varied in type and size. Some



The duration of symptoms for this group was considerably lower than for the group previously considered. In one instance the data relative to the occurrence of the first symptoms were lacking, although this patient underwent, at various hospitals, five operations for recurrence of a parietooccipital tumor. The interval between the first and the second operation was three years and six months, and the interval between the third and the fourth operation was seven months. Of the 13 remaining cases, the average duration of symptoms prior to operation was eighteen months. This includes 4 cases in which the interval between the first symptoms and operation varied from two to five years. In 2 of these 4 cases the tumor was frontal and in 2 it was frontoparietal. Excluding the aforesaid cases, the average duration of symptoms was six months. In 6 of the cases, the duration of symptoms was less than one year.

In 5 instances there were changes in the adjacent bony structures. Primary invasion and perforation of the skull occurred twice, once in a flat tumor in which both an intracranial and an extracranial mass were present, and once in a parasagittal frontal growth which had invaded the frontal and ethmoid sinuses and had caused considerable destruction of the adjacent calvarium. In 2 instances, in both of which the tumor was frontal, erosion of the bone was observed on roentgenographic examination. One growth had caused hyperostosis of the inner table of the frontal bone, and seven years after operation recurrent tumor was present both in the calvarium and beneath the scalp. In the case noted previously with multiple recurrences, invasion of the calvarium and of the mastoid bone was present at the last operation.

*Pathology.*—Of the 14 tumors, 8 were in the frontal or frontoparietal region. Grossly, they varied from moderately well circumscribed global masses to the flat, *en plaque* variety. On the basis of the microscopic appearance the tumors of this group have been separated into two subdivisions. The first group consists of those tumors which, although obviously malignant, have retained certain of the characteristics of the meningotheial tumors; in these the malignancy can be said to be of "parenchymatous" origin. In the second subdivision the tumors can be considered to be sarcoma-like and the tumor tissue of stromal origin. These subdivisions will be considered separately.

There were 6 tumors in the former group. In all of these the tissue appeared to be more or less epithelioid, related to those described by Cushing and Eisenhardt as nonreticulin or collagen-forming epithelioid tumors (Type V). They appeared to have, however, more of the malignant characteristics than the similar growths described in the previous group. The essential microscopic appearance of each of the 6 tumors will be given.

CASE 1.—A large frontal parasagittal tumor was removed from a 38-year-old man. Roentgenographically, there were regions of destruction in the overlying calvarium. Microscopically, the tumor showed definite invasion of the dura mater

CASE 6.—A large parasagittal tumor was situated above the crista galli in a 55 year-old man who had had symptoms for two years prior to operation. At operation the tumor was found to have invaded the frontal and ethmoid sinuses as well as the falx and the longitudinal sinus. Microscopically, the tumor appeared to be intermediate between meningioma and glioma. The cells contained discrete, deeply staining nuclei which varied in size but which were moderately large. There was also considerable variation in cell structure. Some cells appeared polygonal and epithelioid, but elsewhere they were not unlike those of the glioma series. Special stains did not disclose evidence of glial fibers, although the cells were well stained by phosphotungstic acid hematoxylin. There was some tendency toward perivascular arrangement in some regions where the cells appeared more active. Mitotic figures were moderately abundant and there were occasional forms suggestive of giant cells. The tumor contained little stroma and there was definite invasion of the adjacent brain tissue.

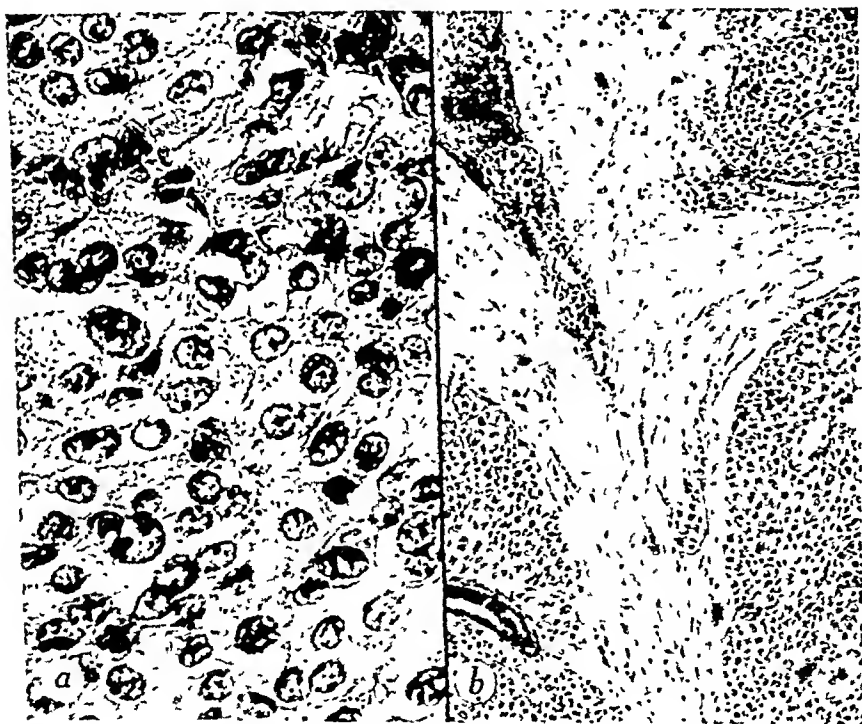


Fig 5—Case 5. Malignant tumor of parenchymatous type, epithelioid variety *a*. High magnification to show the character of the cells. Note the variation in size of both the cells and the nuclei and the numerous mitotic figures in different stages of progression (hematoxylin and eosin  $\times 470$ ). *b*. To illustrate invasion of the brain by tumor. The brain tissue seen in the photograph was completely surrounded by tumor and well within the limits of the growth (hematoxylin and eosin  $\times 55$ ).

There were five highly malignant tumors which were undoubtedly of a sarcomatous type and one growth of a lesser grade of malignancy which appeared to be a fibromyxosarcoma. There was considerable difference in the architecture of these growths and three structural types could be separated. One type appeared to resemble typical fibrosarcoma with streaming cell bundles and a definite tendency toward an interlacing

were elongated and others appeared polygonal. Bizarre, atypical, multinucleated, giant cells were abundant and mitotic figures were frequently encountered. The tumor was vascular.

**CASE 4.**—An extremely large tumor arose from the sphenoid ridge in a 60-year-old woman with symptoms for one year prior to operation. Microscopically, the tumor was very cellular and was composed of small groups and sheets of very large, epithelioid cells (Fig. 4b). There was an occasional suggestion of whorl formation. Reticulin was not present and there was no evidence of collagen formation. The cells contained an abundance of finely granular cytoplasm and large, hyperchromatic, and often pyknotic nuclei. There were no psammoma bodies and only scattered mitotic figures. The tumor was atypical and represented a less malignant form than those already described. Only an occasional giant cell form was seen.

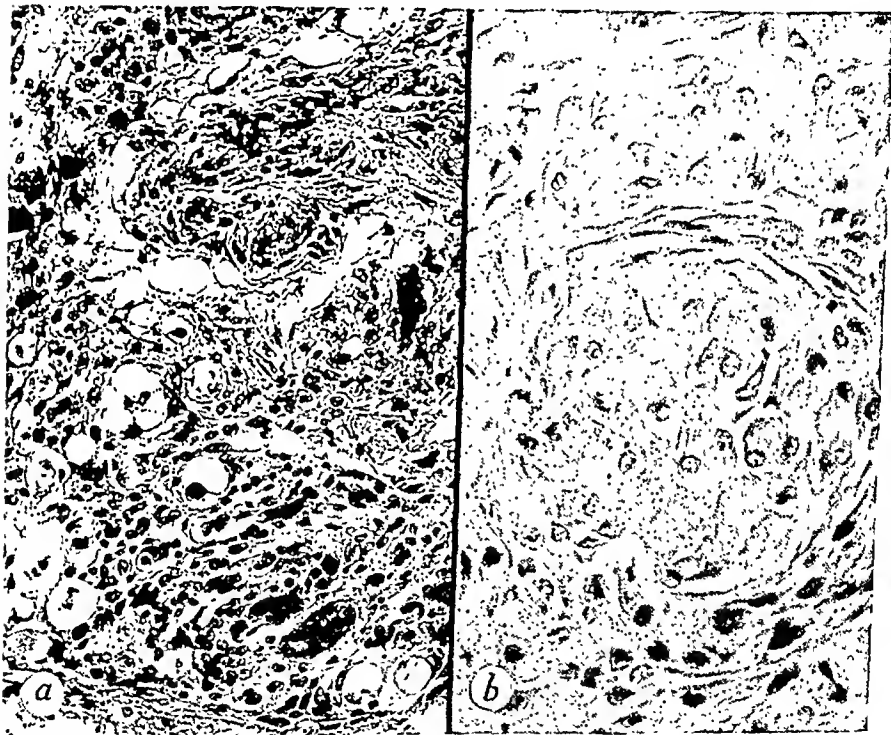


Fig. 4.—Malignant tumors of the *meningioma* type. *a*.—Case 3. To show the marked vascularity of the tumor tissue (hematoxylin and eosin  $\times 220$ ). *b*.—Case 4. To show the variation in the size of the large cells which contain an abundance of finely granular cytoplasm (hematoxylin and eosin  $\times 330$ ).

**CASE 5.**—A tumor was removed from the right occipital region of a 37-year-old man who had had symptoms for sixteen months prior to operation. Recurrence of the growth was evident three years following operation. Microscopically, the tumor was composed of columns and cords of typically epithelioid cells which showed extreme variation in size and shape. Mitotic figures were abundant and there were many atypical giant cell forms (Fig. 5a). Marked invasion of the brain and even of the intrinsic stroma of the tumor was present (Fig. 5b). Some tendency toward a perivascular arrangement of the tumor cells was seen in some portions of the growth. The microscopic appearance was of a highly malignant tumor.

CASE 8.—An extensive tumor arose from the inferior border of the falx at the angle between the falx and the tentorium. The patient was a 32-year-old man and symptoms had been present for six weeks prior to operation. Microscopically, the tumor appeared as a highly cellular growth in which the cells were closely approximated with no characteristic pattern (Fig. 6a). The cells appeared slightly elongated and contained deeply staining nuclei which showed little variation in size or shape. Only occasional giant cells were observed. There was little stroma aside from the presence of a fine intercellular reticulum. There was little degeneration despite only a moderate number of vessels which were rather widely spaced. Mitotic figures were abundant. A section of dura attached to the tumor showed marked invasion. This tumor appeared to be one of the malignant hemangioblastoma group and might be classified as a hemangiosarcoma. It is included in the group of malignant meningiomas for purposes of comparison and to illustrate the occurrence of tumors of vascular origin in the supratentorial region.

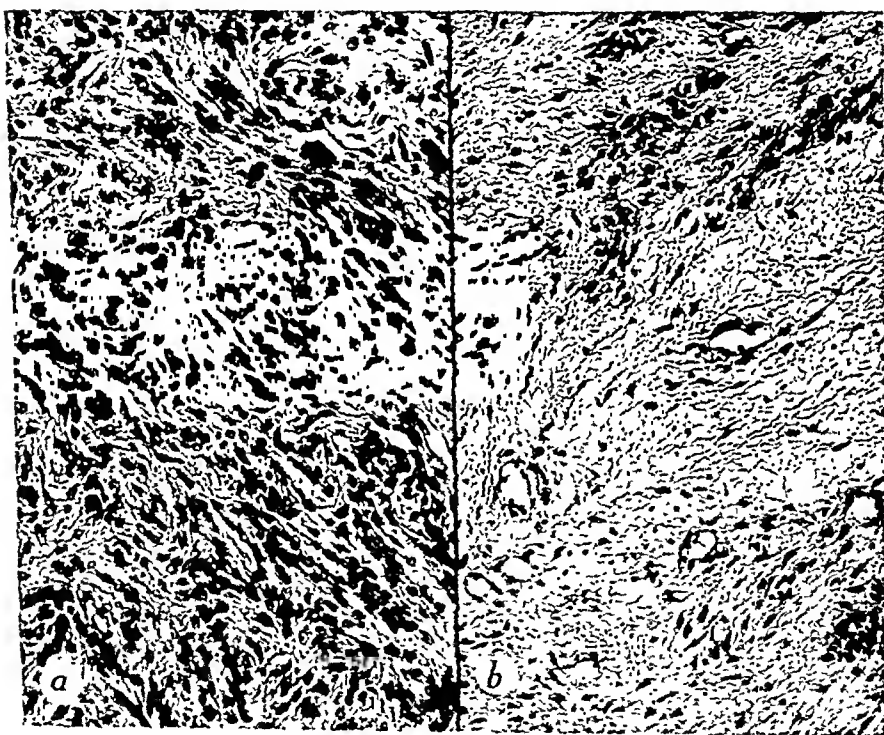


FIG. 6.—a. Case 8. Malignant tumor of stromal origin. Note the cellularity of the tissue and the presence of several giant cells (hematoxylin and eosin  $\times 160$ ). b. Case 9. Malignant tumor of stromal origin. Note the cellular areas separated by numerous small vessels (hematoxylin and eosin  $\times 160$ ).

CASE 9.—A parasagittal tumor measuring 8 by 6 cm. was removed from the frontoparietal region of an 8-year-old boy in whom symptoms had been present for six months prior to operation. Microscopically, the tissue was composed of large cells showing considerable variation in size and an abundance of large, atypical multinucleated giant cells (Fig. 6b). The tissue pattern appeared considerably disorganized, although characteristic streaming was evident throughout. The cell nuclei appeared large, irregular, and hyperchromatic, and mitotic figures

pattern. A second type, apparently closely related to this, was a highly cellular hemangiosarcoma with no definite pattern to the tissue. This type, of which there was one example, appeared to be intermediate between the first type and the Ewing type of growth. The third type was the very active, somewhat atypical tumor of connective tissue origin in which the tissue pattern appeared disorganized and irregular, and which contained many giant cells and abundant mitotic figures. Because of the unusual character of these tumors they will be described individually.

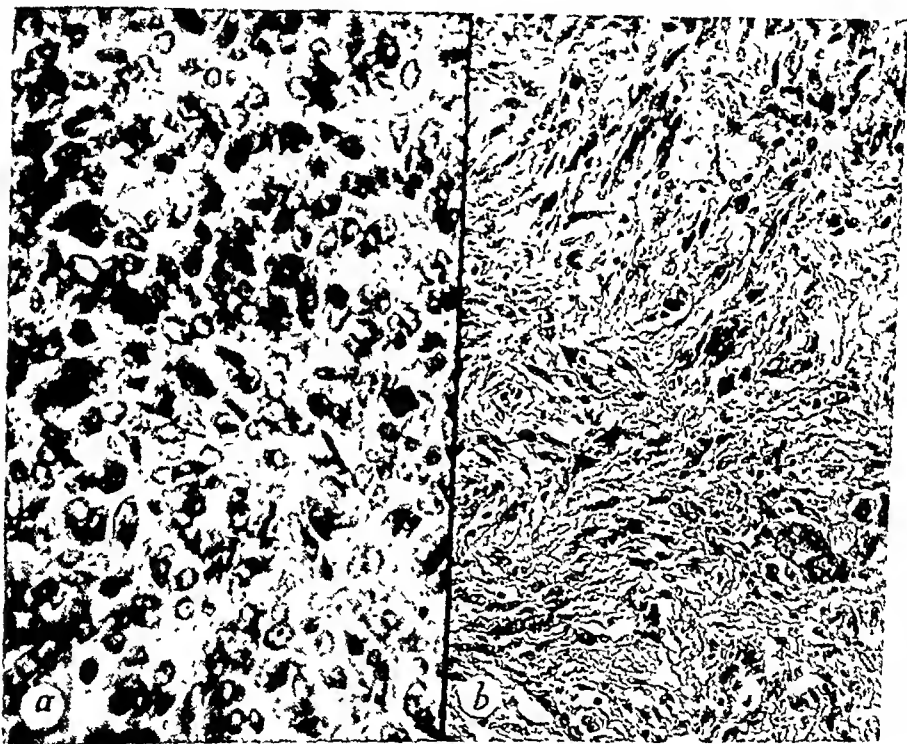


Fig 6.—a, Case 8. Highly malignant malignant tumors of stromal origin or comparison with other malignant tumors of stromal origin of the tissue and the presence of mitotic figures (hematoxylin and eosin  $\times 450$ ). b, Case 9. Rapidly growing tumor of stromal origin. Note the presence of giant cells, tissue pattern (hematoxylin and eosin  $\times 220$ ).

CASE 7.—A specimen from a recurrent parieto occipital tumor was removed from a 47 year old man. This growth has been previously referred to in regard to the numerous and rapid recurrences after removal. Microscopically, the tumor appeared to be a rapidly growing, highly cellular fibrosarcoma. The cells varied in size and shape from those typically fibroblastic to those which appeared but slightly elongated or oval. The nuclei were prominent and chromophilic and there was a moderate number of mitotic figures. In some areas, where the cells appeared elongated, streaming and interlacing of cell bundles occurred, but elsewhere the cells were disposed in sheets. No giant cells were observed. A rather heavy capsule to the tumor showed marked invasion by tumor cells.

compact. In many places giant cells of various types were abundant (Fig. 8a). Some were very large with an abundance of clear, very finely granular cytoplasm and one or two small nuclei. Others were large and irregular in outline with less cytoplasm and four to six very large, irregular nuclei which took the basophilic stain deeply. Mitotic figures were abundant. Degenerative changes were extensive and foci of liquefaction or granular degeneration in many regions caused pseudopalisading of the cells not unlike that seen in glioblastoma multiforme (Fig. 8b). The tissue was vascular, containing many well-formed, small vessels, some of which showed overgrowth of the vessel wall. Calcification or whorl formation was not observed. The tumor had no capsule other than a layer of compressed tumor tissue. Special stains disclosed no glia fibers other than those present as a result of invasion of the contiguous nervous tissue. Comparison of the tissue removed at the two operations revealed no essential difference in the microscopic appearance.

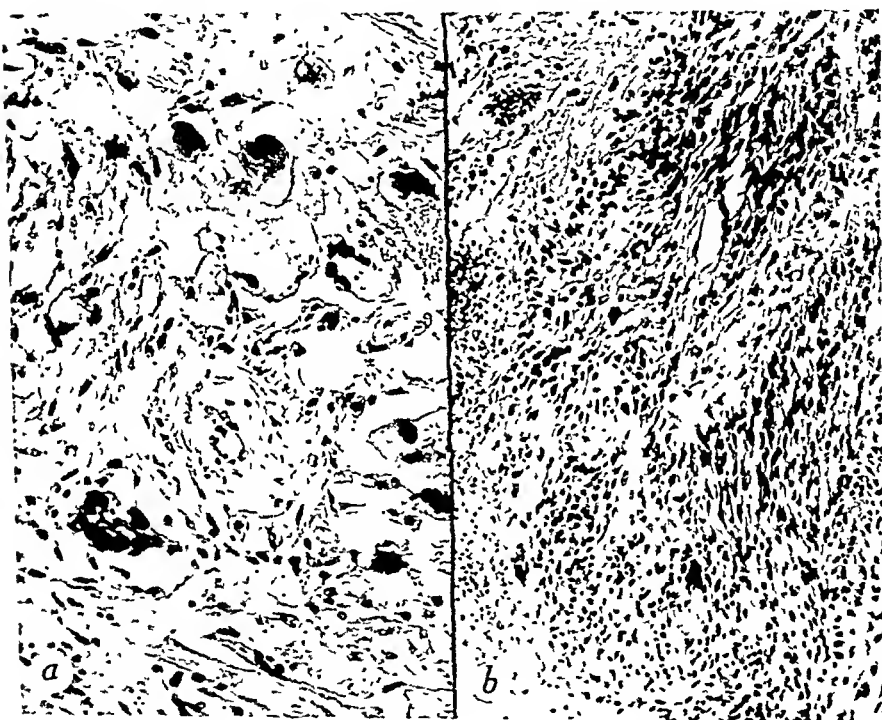


Fig. 8.—Case 13. Highly atypical malignant tumor which had many of the characteristics of glioblastoma multiforme in places, but which was of meningeal origin. *a*, To show the giant cells present (hematoxylin and eosin  $\times 200$ ). *b*, To show the tissue and the tendency toward pseudopalisading due to (hematoxylin and eosin  $\times 130$ ).

The general appearance of this tumor was not unlike that of glioblastoma multiforme with pseudopalisading of the cells, multinucleated giant cells, and overgrowth of the walls of the smaller vessels. However, closer inspection left no doubt as to the meningeal origin of the growth. The clinical course was much as was to be expected from the malignant appearance microscopically.

CASE 14.—A large tumor measuring 10 cm. in diameter was removed from over the right frontal convexity in a 28-year-old woman. Symptoms had been present for three months and roentgenographic examination disclosed erosion of the frontal bone in the region of the growth. Microscopic examination showed the tumor to be

were abundant. The growth is regarded as a highly anaplastic form of malignant meningioma of connective tissue origin.

CASE 10.—A large tumor 8 by 6 cm. in diameter arose in the frontoparietal region of a 40-year-old woman. Symptoms had been present for five years prior to operation. Microscopically, the tissue had an irregular pattern but with some interlacing and streaming of cell bundles (Fig. 7a). The individual cells appeared large and elongated and contained deeply staining nuclei. There was considerable variation in cell size and numerous large multinucleated cells were present. A moderate number of mitotic figures were present. The tissue was cellular and contained many small vessels.

CASE 11.—A growth measuring 10 cm. in diameter was removed from the right prefrontal region of a 37-year-old man who had had symptoms for about two months prior to operation. Recurrence of the tumor was evident about one year after operation. Microscopically, there appeared to be somewhat less streaming than in the other growths. In some regions there was an occasional whorl about vessels. Mitotic figures were present in moderate numbers, as were giant cells. Nuclei appeared large and hyperchromatic. The tissue was quite cellular and highly vascular.

CASE 12.—As has been noted, one growth was classified as a fibromyxosarcoma. This was an hourglass type of tumor removed from the parietal region of a 44-year-old man. He gave a history of having had a small mass, not unlike a sebaceous cyst, over the parietal region for about six weeks prior to admission. At operation this was found to be the extracranial portion of a flattened tumor which had perforated and invaded the skull. The intracranial portion, which apparently had taken origin from the region of the longitudinal sinus, had invaded the dura.

Microscopically, the growth was poorly encapsulated. The tissue was composed of typical elongated fibroblastic cells in large and small groups separated by wide regions of highly myxomatous tissue (Fig. 7b). Mitotic figures were moderately numerous, particularly in the more cellular regions where the tissue had no characteristic pattern for the most part. However, in some portions there was a moderate amount of parallelism and streaming of cell bundles. The growth was extremely vascular, with thin-walled vessels which in some places had the appearance of being formed by the neoplastic cells themselves. In general, the tissue had a loosely woven appearance and this was true even of the more cellular portions.

#### ATYPICAL TUMORS OF UNCERTAIN ORIGIN

There were two growths which, although of undoubtedly meningeal origin, were highly atypical and which because of their unusual character were not placed in either of the preceding two groups. Although both of these tumors were probably of stromal origin, they showed sufficient variation from those previously described to allow being considered separately.

CASE 13.—A left basofrontal tumor measuring 6 cm. in diameter was removed from a 49-year-old man who had had symptoms for seven months prior to the first operation. Evidence of recurrence of the growth was present eight and one-half months after operation despite radiation in the interval. At the second operation, eleven months after the first, the tumor was found to have extended bilaterally. Microscopically, the tissue appeared quite atypical and varied considerably in different portions of the tumor. For the most part, the individual cells were elongated and spindle-shaped, containing rather large, chromophilic nuclei which varied moderately in size. In some regions the cells were disposed in sheets, but elsewhere the tissue was irregular with some interlacing of cell bundles. Here the tissue appeared quite

in 1934, reported briefly a case of "spindle-cell sarcoma of the dura" in the hypophyseal region in which death occurred four months following the appearance of the first symptom. At necropsy, three round, nodular, metastatic tumors were found in the liver, the largest the size of a walnut. The second case referred to was that reported by Foot and Zeek.<sup>18</sup> The patient was a 45-year-old man who died six weeks after the first symptom from a melanoma arising in the meninges of the right temporal region. At necropsy a dozen melanotic nodules were found in the lungs and the intracranial tumor was considered to be the primary lesion after a careful search had failed to disclose any other possible primary site. In both instances noted, operation had not been performed and irradiation had not been given.

Distant subarachnoid and intraventricular implants are not to be included under the heading of metastasis and should be looked on as "seeding," a process essentially different from the pathologic viewpoint. Such remote implantation of tumor is the result of the dissemination of viable tumor fragments by the cerebrospinal fluid and is frequently seen in medulloblastoma and choroid plexus papilloma and less frequently in other gliomas. In general, the property of giving rise to distant metastasis, which has been termed one of the cardinal properties of the malignant tumor, is rarely encountered in the meningeal growths, despite the degree to which other evidences of malignancy may be present. In none of the highly malignant tumors described here were there any associated secondary growths outside of the nervous system.

The general conception, frequently quoted in textbooks, is that the meningiomas rarely if ever invade the brain but rather compress it in the process of expansion. Nevertheless, Globus has stated, "It is necessary to correct at this point a statement made frequently that the meningioma never passes beyond the pial barrier and never penetrates the brain. In the large number of the tumors investigated in this study, the tumor had invaded the brain tissue to variable depths." This has also been found true in the present study. Reference must be made to the tendency noted by Cushing and others for meningiomas to recur after a variable time, despite what at the time of operation appeared to be a complete removal of the tumor. This indicates that many of these tumors are less encapsulated and less sharply defined from the adjacent cerebral tissue than would appear grossly, and reappearance of the growth must be considered as continuance rather than recurrence of the tumor. In certain instances, particularly if there has been piecemeal removal or if the tumor has been broken across in the process of removal, the meningiomas exhibit a tendency to seed in the adjacent muscle or scalp. Although this cannot be looked on as certain evidence of malignancy, it indicates a decided activity on the part of the tumor,



composed of moderately large, slightly elongated cells which were irregularly disposed, at times in columns and cords, between strands of connective tissue. The nuclei were somewhat irregular in shape and showed considerable variation in size (Fig. 9). In some regions invasion of the larger connective tissue strands by tumor cells was apparent. A coarse reticulum was present between the cells and cell groups. There were no giant cells, but mitotic figures were present in large numbers throughout the tissue. There was some evidence of invasion of the adjacent cerebral tissue, but from the surgical specimen this was not certain.

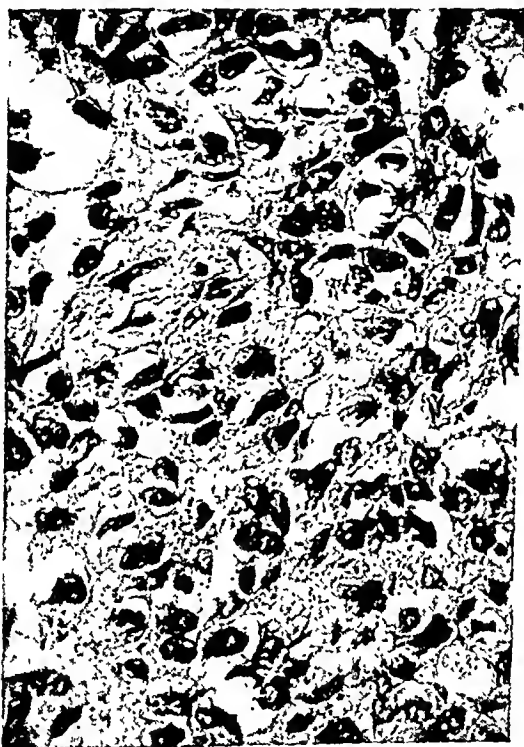


Fig. 9.—Case 14. Atypical, highly malignant tumor, probably of stromal origin, removed at operation. Note the irregularity of the tissue and the variation in cell and nuclear size. Mitotic figures are present (hematoxylin and eosin  $\times 365$ ).

#### COMMENT

The concept of the malignant tumor as an autonomous, invasive growth capable of giving rise to distant metastases requires some revision in respect to the malignant meningiomas and, indeed, in respect to most of the tumors arising within the cranial cavity. It is generally believed that intracranial tumors do not metastasize outside of the cranial and spinal chambers, and a survey of the literature discloses few instances in which an intracranial growth has given rise to a similar lesion outside of the nervous system. Nelson,<sup>16</sup> in 1936, was able to find in the literature for ten years prior to the publication of his article 7 reports of metastasizing intracranial tumors. Of these, 2 cases could be considered to fall within the group of meningeal tumors. Brandt,<sup>17</sup>

these tumors of advanced malignancy do not differ clinically in their various types, but rather in their microscopic appearance. Inasmuch as they must be included under the group of meningiomas, it seems best to designate them as malignant meningiomas, indicating a specific variety with an essential origin from the meninges rather than as sarcomas, with which term the significance of their origin is lost. At the same time, the use of the descriptive term contrasts them with the ordinary benign variety of meningioma.

#### CONCLUSIONS

1. About 10 per cent of all meningeal tumors arising within the cranial cavity are microscopically malignant when judged by the type of cells, the architecture of the tissue, and the presence of giant cell forms and mitotic figures.

2. The malignant meningeal tumors may be divided into those which are of early or low-grade malignancy and those which are of advanced or high-grade malignancy. This differentiation is reflected in the changes in the architecture of the tissue in the low-grade malignant tumors and in the changes both in the cell type and structure and in the tissue architecture in the tumors of advanced malignancy.

3. The classification and differentiation of the various morphologic forms of these malignant tumors are based on the concept of these tumors as variations and admixtures of structural elements of two types. The epithelioid type of tissue forms one extreme and the fibroblastic or stromal type of tissue forms the other extreme. Thus, the tumors can be considered to be of parenchymatous or of stromal origin, and mixtures of the two types may occur in any one tumor.

4. Malignancy in these meningeal tumors tends to accentuate the character of the predominant type of tissue, whether it is of the parenchymatous or of the stromal variety.

5. Variations in structure in each of the types of the tumors of advanced malignancy are due in part to the anaplastic process with progression beyond that of simple malignant change.

6. The term malignant meningioma is to be preferred to the term sarcoma, which might be applied to some of these growths. The former indicates a specific variety of tumor with an essential origin from the meninges and contrasts these tumors with the ordinary benign meningiomas.

7. There is, in the main, a close correlation between the microscopic grade of malignancy and the clinical course when the duration of symptoms, size of the growth, and location are all taken into account.

#### REFERENCES

1. Bailey, Percival, and Bucy, P. C.: The Origin and Nature of Meningeal Tumors, *Am. J. Cancer* 15: 15-51, 1931.

certainly not present in all the meningiomas. Cushing and Eisenhardt cited several instances of this, some of them in the variety which they described as malignant.

Oertell's<sup>19</sup> conception in reducing the factors of lawlessness and malignancy in cancer to terms of "intensity or tempo of growth" is particularly adaptable to the first group of tumors described here, those of low-grade or early malignancy. Craig, in his discussion of the malignant meningiomas, noted three stages in the metamorphosis of a benign to a malignant tumor: (1) hypertrophy of the cells, (2) hyperplasia or an increase of embryonic undifferentiated cells, and (3) the migration or invasion of the surrounding tissue by embryonic cells. He graded the tumors on the basis of cellular differentiation, mitotic figures, and the general tissue structure, and noted that in those meningiomas in which the grade of malignancy was low, whorl formation was observed. In the present study, whorl formation was seen infrequently in the first group and with rare exception it was absent in the tumors of advanced malignancy.

As Foot<sup>20</sup> has noted, the classification of the meningiomas based on the histologic nature of the tumors may be considered as variations in structure from the epithelioid type at one end to the purely fibroblastic or stromal variety at the other end. This conception of the meningiomas as compound tumors explains the variety of forms in both the benign and the malignant group in which either the parenchymatous or the stromal elements may predominate or compose the entire growth. It appears to be a characteristic of the malignant meningiomas that the composite makeup of the tumor tissue is lost or minimized with one of the elements, either the parenchymatous or the stromal, predominating in the final picture. Thus, malignancy appears to accentuate the type of growth whether it be of meningocytic origin, derived presumably from the arachnoid villi, or of stromal or fibroblastic origin, derived from the pia-arachnoid. In many instances, however, although one may predominate, remnants or indications of the association of the other may be found on careful examination.

The frequent bizarre and atypical forms which are encountered are to be considered as the progress of the anaplastic process beyond the stage of simple development of sarcomatous or malignant properties. The giant cells, frequently seen in the more malignant of the tumors described here, were considered by Globus as evidence of vigorous cell growth. Globus considered these cells as establishing a link between the meningiomas of quiescent type and those acquiring malignant character. It is to be noted that in many of the tumors of low-grade or early malignancy, early or incomplete forms of giant cells were noted.

Some mention must be made of the use of the term malignant meningioma in preference to the term sarcoma which might be applied to some of these growths. As far as can be determined at the present time,

these tumors of advanced malignancy do not differ clinically in their various types, but rather in their microscopic appearance. Inasmuch as they must be included under the group of meningiomas, it seems best to designate them as malignant meningiomas, indicating a specific variety with an essential origin from the meninges rather than as sarcomas, with which term the significance of their origin is lost. At the same time, the use of the descriptive term contrasts them with the ordinary benign variety of meningioma.

### CONCLUSIONS

1. About 10 per cent of all meningeal tumors arising within the cranial cavity are microscopically malignant when judged by the type of cells, the architecture of the tissue, and the presence of giant cell forms and mitotic figures.

2. The malignant meningeal tumors may be divided into those which are of early or low-grade malignancy and those which are of advanced or high-grade malignancy. This differentiation is reflected in the changes in the architecture of the tissue in the low-grade malignant tumors and in the changes both in the cell type and structure and in the tissue architecture in the tumors of advanced malignancy.

3. The classification and differentiation of the various morphologic forms of these malignant tumors are based on the concept of these tumors as variations and admixtures of structural elements of two types. The epithelioid type of tissue forms one extreme and the fibroblastic or stromal type of tissue forms the other extreme. Thus, the tumors can be considered to be of parenchymatous or of stromal origin, and mixtures of the two types may occur in any one tumor.

4. Malignancy in these meningeal tumors tends to accentuate the character of the predominant type of tissue, whether it is of the parenchymatous or of the stromal variety.

5. Variations in structure in each of the types of the tumors of advanced malignancy are due in part to the anaplastic process with progression beyond that of simple malignant change.

6. The term malignant meningioma is to be preferred to the term sarcoma, which might be applied to some of these growths. The former indicates a specific variety of tumor with an essential origin from the meninges and contrasts these tumors with the ordinary benign meningiomas.

7. There is, in the main, a close correlation between the microscopic grade of malignancy and the clinical course when the duration of symptoms, size of the growth, and location are all taken into account.

### REFERENCES

1. Bailey, Percival, and Bucy, P. C.: The Origin and Nature of Meningeal Tumors, *Ann. J. Cancer* 15: 15-31, 1931.

2. Cushing, Harvey, and Eisenhardt, Louise: *Meningiomas; Their Classification, Regional Behaviour, Life History, and Surgical End Results*, Springfield, Ill., 1938, Charles C Thomas, Publisher, 785 pp.
3. Baker, A. B.: *Intracranial Tumors: A Study of 467 Histologically Verified Cases*, Minnesota Med. 23: 696 703, 1940.
4. Globus, J. H.: *The Meningiomas: Their Origin, Divergence in Structure, and Relationship to the Brain in the Light of the Phylogenesis and Ontogenesis of the Brain: A Suggestion of a Simplified Classification of Meningeal Neoplasms*, Proc. A. Research Nerv. & Ment. Dis (1935) 16: 210 265, 1937.
5. Craig, W. McK.: *Malignant Intracranial Endotheliomata*, Surg., Gynec. & Obst. 45: 760 768, 1927.
6. Penfield, Wilder, Erickson, T. C., and Tarlov, I.: *Relation of Intracranial Tumors and Symptomatic Epilepsy*, Arch. Neurol. & Psychiat. 44: 300 315, 1940.
7. Frazier, C. A. and Alpers, B. J.: *Meningeal Fibroblastomas of the Cerebrum; a Choneopathologic Analysis of Seventy Five Cases*, Arch. Neurol. & Psychiat. 29: 935 989, 1933.
8. Bailey, Percival: *Intracranial Sarcomatous Tumors of Leptomeningeal Origin*, Arch. Surg. 18: 1359 1402, 1929.
9. Turner, O. A., and Craig, W. McK.: Unpublished data.
10. Hsu, Y. K.: *Primary Intracranial Sarcomas*, Arch. Neurol. & Psychiat. 43: 901 924, 1940.
11. Akelaitis, A. J. E.: *Primary Melanosarcoma of the Leptomeninges*, Am. J. Path. 11: 591-610, 1935.
12. Kessler, M. M.: *Melanoblastosis and Melanoblastoma; Primary and Secondary Involvement of the Brain; Anatomie Study*, Am. J. Cancer 30: 19 31, 1937.
13. Yuile, C. L.: *Case of Primary Reticulum Cell Sarcoma of the Brain, Relationship of Microglia Cells to Histiocytes*, Arch. Path. 26: 1036 1044, 1938.
14. Mallory, T. B.: *Pathologic Discussion*, New England J. Med. 203: 177, 1930.
15. Cottrell, Lillian: *Primary Fibrosarcoma of the Brain*, Arch. Path. 27: 895 901, 1939.
16. Nelson, A. A.: *Metastases of Intracranial Tumors*, Am. J. Cancer 28: 1 12, 1936.
17. Brandt, M.: Quoted by Nelson, A. A.<sup>16</sup>
18. Foot, N. C., and Zeek, Pearl: *Two Cases of Melanoma of the Meninges With Autopsy*, Am. J. Path. 7: 605 616, 1931.
19. Oertell, Horst: *The "Romantic" Attributes of "Lawlessness" and "Malignancy" in Cancer*, Am. J. M. Sc. 197: 1 7, 1939.
20. Foot, N. C.: *Meningioma*, Arch. Path. 30: 198 211, 1940.

## THROMBOANGIITIS OBLITERANS\*

### CLINICAL OBSERVATIONS AND ARTERIAL BLOOD OXYGEN STUDIES DURING TREATMENT OF THE DISEASE WITH SODIUM TETRATHIONATE AND SODIUM THIOSULFATE

FRANK V. THIEIS, M.D., AND M. R. FREELAND, PH.D., CHICAGO, ILL.

(From the Departments of Surgery, Rush Medical College of the University of Illinois and the Presbyterian Hospital)

IN THE treatment of thromboangiitis obliterans consideration should be given to the three factors in the pathology of the disease: (1) biochemical blood changes; (2) peripheral thromboses resulting in circulatory deficiency, infarcts, and gangrene; and (3) local infection. For the pathologic blood condition<sup>1</sup> we have used intravenous injections of sodium tetrathionate ( $\text{Na}_2\text{S}_4\text{O}_{10} \cdot \text{H}_2\text{O}$ ) and sodium thiosulfate ( $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ ).<sup>2</sup> Pavaex treatment<sup>3</sup> is indicated for the circulatory deficiency resulting from arterial thromboses. Local infection of the peripheral tissues is usually treated with hypertonic (25 per cent) magnesium sulfate dressings. Because of the success in the treatment of thromboangiitis obliterans with the inorganic sulfur compounds some of our clinical observations and results of arterial blood oxygen studies are herewith reported.

The following cases illustrate the clinical course of the disease and the changes in the arterial blood oxygen which followed treatment. The patients were divided into two groups: (1) without infection and (2) with infection. Oscillometric and stabilized peripheral temperature readings were taken on all patients. Although the biochemical blood changes which followed treatment were fairly constant in the two groups, the clinical course differed because of the infection.

#### THROMBOANGIITIS OBLITERANS WITHOUT INFECTION

CASE 1.—Mr. N., aged 23 years, of Norwegian descent, was first examined June 7, 1934, suffering with thromboangiitis obliterans of all four extremities of three years' duration. An excruciatingly painful ulcer about the size of a quarter on the right first toe had been present for three months. There was no infection. Constant rest pains and intermittent claudication (one half block) had forced him to give up his work as a patternmaker. The oscillometric index of the right ankle and that of both wrists were almost zero (Fig. 1). He was a heavy cigarette smoker.

Biweekly injections of sodium thio-sulfate were followed in six weeks by complete relief from rest pains and improvement in the intermittent claudication and ulcer. Despite the improvement and gain of thirty five pounds in weight the temperature of the toes remained unchanged for more than two months. Pavaex treatment for

\*Presented before the Central Surgical Association March 1, 1941, at Ann Arbor, Mich.

Received for publication, April 2, 1941

the organic occlusion in the peripheral arteries was then started and was followed by rapid elevation in skin temperatures and the ulcer healed (Fig. 2). After periodically continuing biweekly injections for three years he has remained in excellent health without further treatment (four years) although he is still smoking moderately.

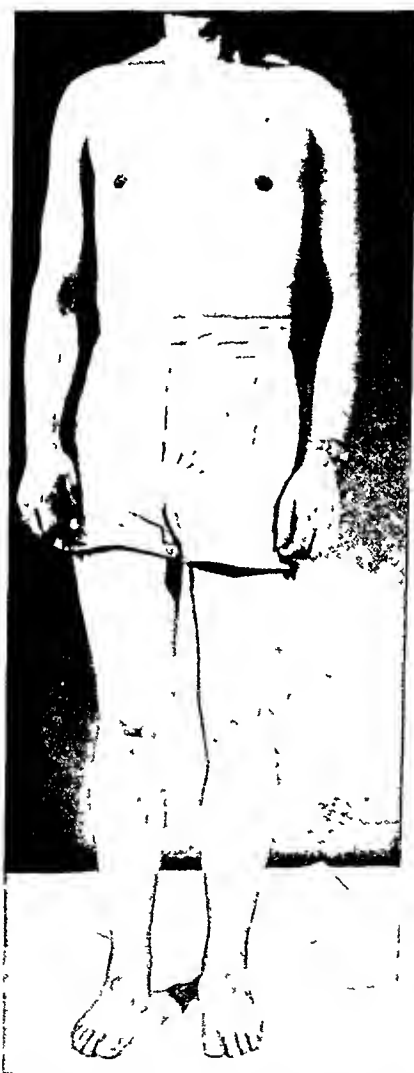


Fig. 1—Patient clinically well for more than six years after treatment for acute thromboangitis obliterans (Case 1). All four extremities were involved. Relief from the severe rest pains in the right foot and healing of a gangrenous infarct of the first toe were independent of changes in the peripheral temperatures (Fig. 2).

During the course of treatment the erythrocyte count varied from 4.4 to 7.5 million and the hemoglobin index from 67 to 85 per cent. The normal relation between the colorimetric hemoglobin index and the oxygen capacity did not exist. After months of no treatment and of heavy smoking, an injection of sodium thio-sulfate increased the oxygen capacity from 20 to 24 volumes per cent with an erythrocyte count of 5.7 millions and colorimetric hemoglobin value of 85 per cent remaining

unchanged. One year later when the patient was clinically well but still smoking moderately the effect on the oxygenation of the arterial blood of smoking two cigarettes was as follows:

	OXYGEN		CARBON-DIOXIDE
	CAPACITY VOLUMES %	SATURATION %	CONTENT VOLUMES %
Arterial blood			
June 28, 1937: Receiving treatment, smoking moderately			
Before smoking	17.99	93.15	47.08
After smoking two cigarettes	17.22	88.00	46.92

*Comment.*—Clinical improvement with complete relief from rest pains and healing of a noninfected ulcer of the toe followed twelve biweekly injections of sodium thiosulfate. The peripheral skin temperatures remained unchanged for two months. Pavaex treatment rapidly elevated the temperatures to the normal level. While the patient was clinically well, although continuing to smoke moderately, the oxygen saturation of the arterial blood was reduced 5 per cent by smoking two successive cigarettes. This reduction did not occur in more than fourteen control patients but was observed in other patients with thromboangiitis obliterans.

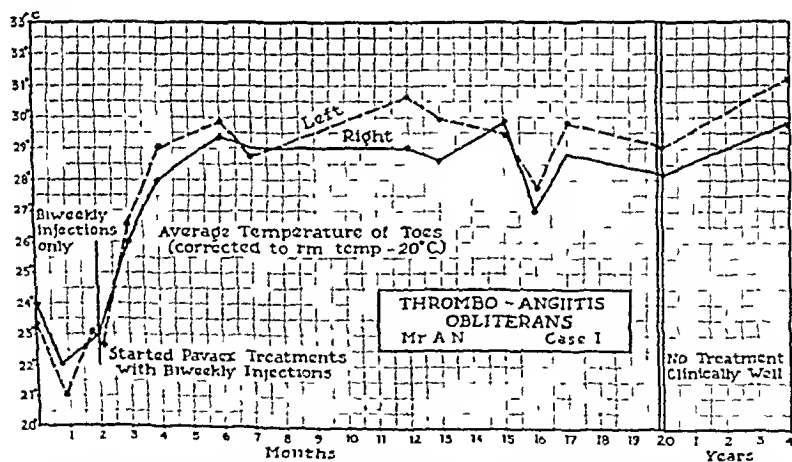


Fig. 2—Complete relief from rest pains (Fig. 1, Case 1) followed treatment of the pathologic blood condition with biweekly injections of sodium thiosulfate for six weeks. Despite the marked clinical improvement the peripheral skin temperatures remained unchanged. Rapid elevation of skin temperatures followed pavaex treatment.

*CASE 2.*—Mr. M., aged 43 years, a Mexican freight handler, was admitted on Oct. 20, 1934, suffering with severe intermittent claudication (one block) and rest pains of the right leg. Since December, 1933, when he thought that he had frozen the right foot, the symptoms had become progressively worse. He had been a heavy smoker of Mexican cigarettes.

He remained in the hospital for four days but continued biweekly injections of sodium thiosulfate for six weeks. Complete relief from pain and elevation of skin temperatures followed treatment. Although he resumed heavy smoking he remained completely comfortable. He was then unable to return for three weeks



because of inclement weather. Two days before his readmission on Dec. 20, 1934, all the previous symptoms recurred and the right second toe suddenly became black and excruciatingly painful.

For two months other forms of treatment without the inorganic sulfur compounds were used without relief from pain. From 6,000 to 8,000 c.c. of Ringer's solution was given daily for four weeks. Badly infected teeth were extracted and bacterial filtrates of *Streptococcus viridans* were obtained and given intradermally

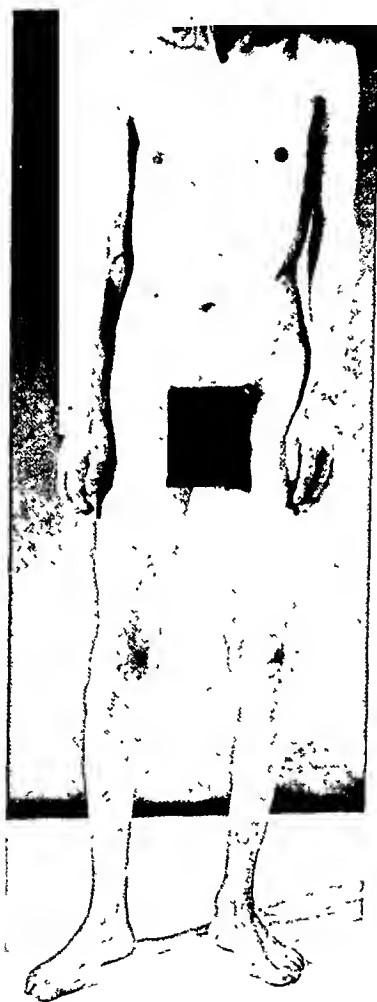


Fig. 3.—Patient clinically well (December, 1934) after numerous recurrences of gangrenous ulcerations. Despite increase in peripheral temperature of the toes of  $6^{\circ}$  C. following other forms of treatment for two months, relief from pain did not occur until two weeks after treatment with sodium thiosulfate was resumed (Case 2).

without effect. Despite the lack of subjective relief the peripheral temperatures increased  $6^{\circ}$  C. Prompt relief from pain followed daily injections of sodium thiosulfate for two weeks when the gangrenous toe was amputated. Complete recovery was rapid and he gained twenty pounds in weight (Fig. 3).

After resuming heavy smoking and discontinuing treatment for six months the disease recurred in both hands (Fig. 4) although the legs have remained in excellent

condition (six years). He is now enjoying fairly good health with periodic treatment although he has numerous finger deformities as a result of the disease.

The oxygen saturation of the arterial blood during a period of treatment and complete abstinence from smoking was considerably below the normal level. The initial effect of smoking was an increase in the oxygen saturation:

	OXYGEN		CARBON-DIOXIDE
	CAPACITY VOLUMES %	SATURATION %	CONTENT VOLUMES %
Arterial blood			
Jan. 27, 1938: Clinically improved, no smoking or treatment for some months			
Before smoking	18.66	80.95	49.91
After smoking one cigarette	18.27	92.12	49.56



Fig. 4.—Marked clinical improvement occurred after involvement of both lower extremities. Six months later, infected infarcts occurred in the fingers of both hands (Case 2) after resumption of heavy smoking and discontinuing treatment.

*Comment.*—The first acute attack of thromboangiitis obliterans with impending gangrene was relieved within six weeks by intravenous sodium thiosulfate. Recurrence followed discontinuance of treatment and resumption of heavy smoking. Other forms of treatment were then used for two months without relieving the severe rest pains despite increased peripheral temperatures of  $6^{\circ}\text{C}$ . The pains were relieved within two weeks after resumption of the inorganic sulfur therapy. While clinically well and not smoking the low percentage of oxygen saturation of the arterial blood was increased to the normal level (Table I) by smoking one cigarette. This initial effect was accompanied by elevation in blood pressure, increased pulse rate, and peripheral vasoconstriction. The systemic need for these responses may explain the almost uncontrollable desire of patients with thromboangiitis obliterans to smoke.

TABLE I  
ARTERIAL BLOOD, OXYGEN CAPACITY AND OXYGEN SATURATION

	NO. CASES	NO. DETERMINA- TIONS	OXYGEN CAPACITY VOLUME PER CENT			OXYGEN SATURATION PER CENT		
			MAXIMUM	MINIMUM	AVERAGE	MAXIMUM	MINIMUM	AVERAGE
Controls	20	30	20.96	17.50	18.72	96.60	88.20	92.45
Males	15	22	20.96	17.50	18.91	96.60	88.20	92.29
Females	5	8	18.82	17.69	18.44	96.40	88.60	92.66
Thrombangiitis obliterans	22	48	21.50	11.00	17.46	101.30	54.70	88.49
No treatment { Not smoking (?)	6	8	18.96	14.20	17.10	81.20	54.70	74.28
{ Heavy smoking	2	3	11.68	11.00	13.40	96.10	87.40	92.50
Neurocirculatory	11	29	20.00	14.52	16.72	98.70	79.40	91.00
Males	5	14	20.00	14.52	17.11	98.70	83.80	91.02
Females	6	15	17.36	14.70	16.26	96.90	79.40	91.01
Raynaud's disease	3	6	17.36	15.90	16.50	95.50	79.40	88.34
Arteriosclerosis	6	9	19.61	15.75	16.92	98.65	87.04	92.19
Polycythemia vera	1	4	25.50	22.20	22.90	99.36	75.90	83.99

CASE 3.—Mr. K., aged 48 years, a gentile grocery store clerk, was referred April 17, 1939, because of a previously diagnosed thromboangiitis obliterans of the left foot and leg. In May, 1937, the right leg was amputated elsewhere. Following resumption of smoking, pains, coldness, and discoloration developed in the left foot. Pulsations were palpable in the dorsalis pedis, posterior tibial and popliteal arteries. No treatment or further examination was made at this time.

He returned on July 27, 1939, with the arterial pulsations in the foot no longer palpable. Oscillometric index at the ankle was zero. The blood examination showed erythrocyte count of 4,550,000, hemoglobin index of 78 per cent, and leucocyte count of 7,450. These blood findings were associated with the following initial oxygen capacities of the blood:

	OXYGEN		CARBON-DIOXIDE	
	CAPACITY VOLUMES %	SATURATION %	CONTENT VOLUMES %	
Arterial blood				
July 27, 1939:				
Before injection	11.00	96.10	45.80	
After 0.6 Gm. sodium tetrathionate	11.70	87.40	44.30	
Aug. 10, 1939: No treatment since				
July 27, 1939				
Before injection	17.60	96.10	44.70	
After 0.6 Gm. sodium tetrathionate	17.60	90.30	43.90	

Bi-weekly injections were continued for one month when he reported that he was feeling much better and had gained ten pounds in weight. It is doubtful that he had discontinued smoking.

*Comment.*—Clinical improvement which followed intravenous sodium tetrathionate was accompanied by marked increase in the oxygen capacity of the arterial blood. The initial oxygen capacity was far below the normal level. The colorimetric hemoglobin index and erythrocyte count remained unchanged despite the marked increase in oxygen capacity two weeks after one injection of sodium tetrathionate.

CASE 4.—Mr. H., aged 63 years, a retired American gentile salesman, was admitted Jan. 29, 1940, suffering with advanced bilateral thromboangiitis obliterans. Oscillometric readings of both lower legs were almost zero. Roentgenograms were negative for arteriosclerosis. He was an unusually heavy cigarette and pipe smoker. Biweekly injections of sodium tetrathionate were followed by marked improvement in the biochemistry of the blood and in the clinical symptoms. At the present time (February, 1941) he walks five to six blocks without distress and feels well.

The results of the blood oxygen studies were as follows:

	OXYGEN		CARBON-DIOXIDE	
	CAPACITY VOLUMES %	SATURATION %	CONTENT VOLUMES %	
Arterial blood				
Feb. 11, 1940: Initial, new case, curtailed smoking 1 wk.				
Before injection	11.70	67.80	48.60	
After 0.4 Gm. sodium tetrathionate	14.70	67.10	48.60	
April 23, 1940: Biweekly injections	14.60	96.10	49.60	
Oct. 31, 1940: Biweekly injections	14.67	94.20	47.00	

The increased oxygenation of the arterial blood from 67 to 96 per cent was accompanied by marked improvement in the initially elevated blood sugar, cholesterol and cholesterol esters, total fatty acids, and low glutathione.

*Comment.*—Marked clinical improvement followed biweekly injections of sodium tetrathionate. The initial low percentage of oxygen saturation of the arterial blood increased to the normal level. The oxygen capacity remained unchanged and below normal for the colorimetric hemoglobin value which was present.

CASE 5.—Mr. B., aged 42 years, a gentle salesman, was admitted to the hospital April 17, 1939, suffering with bilateral thromboangiitis obliterans of both lower extremities. For years he smoked two to three packages of cigarettes daily and he was a heavy drinker. Daily injections of sodium tetrathionate and pavaex treatment resulted in relief from pain within three weeks. This was accompanied by rapid improvement in the sedimentation time of the blood (Table II).

TABLE II

TIME FOR 18 MM. OF CELLS (LINZENMEIER METHOD)			REMARKS
April 18, 1939	25 min.	}	Intensive treatment ( $\text{Na}_2\text{S}_2\text{O}_6 \cdot \text{H}_2\text{O}$ ) started
April 19, 1939	30 min.		
April 24, 1939	30 min.		
April 29, 1939	35 min.		
May 6, 1939	1 hr. 15 min.		
May 14, 1939	2 hr. 55 min.	}	Normal values
May 21, 1939	4 hr. 25 min.		
June 10, 1939	6 hr. 10 min.		
July 22, 1939	4 hr. 30 min.		Resumed heavy smoking; recurrence
Nov. 3, 1939	1 hr. 20 min.		
Dec. 2, 1939	1 hr. 20 min.		
Jan. 24, 1940	6 hr. 00 min.		Intensive treatment ( $\text{Na}_2\text{S}_2\text{O}_6 \cdot \text{H}_2\text{O}$ )
Feb. 2, 1940	4 hr. 00 min.		
Feb. 24, 1940	4 hr. 30 min.		
March 23, 1940	6 hr. 35 min.		

The oxygenation of the arterial blood was as follows:

	OXYGEN		CARBON-DIOXIDE	
	CAPACITY VOLUMES	SATURATION %	CONTENT VOLUMES	%
Arterial bloods				
April 19, 1939: Initial, heavy smoker	14.29	81.20	47.10	
Smoked two cigarettes	14.36	87.10	45.70	
Smoked four cigarettes	14.61	86.20	46.40	
July 22, 1940: Bi-weekly injections				
Before injection	20.00	91.40	38.50	
After 0.6 Gm. sodium tetrathionate	20.20	94.20	39.00	

*Comment.*—Marked clinical improvement with complete relief from rest pains followed three weeks' treatment with sodium tetrathionate. The initial low percentage of oxygen saturation and oxygen capacity increased to the normal levels. The gradual improvement in the initial rapid sedimentation rate of the blood during treatment is shown in Table II. There was no ulceration or infection present.

## THROMBOANGITIS OBLITERANS WITH SECONDARY INFECTION

Bacteriologic studies of smears and cultures obtained from ulcerated or infected areas failed to account for the unusual features of these infections. A number of aerobic organisms were present either in pure culture or in a mixed infection. No anaerobic growths were obtained. *Streptococcus viridans* and *Staphylococcus aureus* were most frequently found, although organisms of *Escherichia*, *Pseudomonas*, *Staphylococcus albus*, and *Corynebacterium* groups were occasionally present. An excised thrombosed dorsalis pedis artery (Case 1) did not produce bacterial growth on a number of culture media.

CASE 6.—Mr. L., aged 46 years, a Russian Jew, was first examined March 4, 1940, having suffered with bilateral thromboangitis obliterans of the lower extremities since 1930. During the ten-year period he had elsewhere bilateral cervical and lumbar sympathectomy and nine peripheral nerve operations. Amputation of the right leg was refused and he came to us for treatment. For more than twenty five years he had consumed more than two packages of cigarettes daily.

On admission to the Presbyterian Hospital he was bedridden with an infected ulcerated right foot and first toe (Fig 5). Extreme unrelenting rest pains were present for weeks. Six weeks of daily injections of sodium tetrathionate were followed by marked improvement in the pain and infection. On April 17, 1940, a wedge-shaped resection of the toes was performed because of extensive osteomyelitic destruction of the bones. He was discharged on April 29, 1940, and periodically since then he has received biweekly injections and pavaex treatment (Fig 6). Although the operative wound was slow in healing and he sometimes has burning pain in the healed first toe, he is now active and enjoying fairly good health (one year).

Arterial blood oxygen determinations were made four months after discontinuance of smoking and treatment.

		OXYGEN		CARBON DIOXIDE
		CAPACITY	SATURATION	CONTENT
		VOLUMES %	%	VOLUMES %
Arterial blood				
Oct. 17, 1940 No treatment or smoking				
for 4 mo				
Before injection		17.55	54.70	51.20
After 0.6 Gm sodium tetrathionate		18.96	67.10	38.50
Dec. 5, 1940 Biweekly injections of				
sodium tetrathionate				
Dec. 19, 1940		17.6	90.0	39.80
No treatment 2 w		16.20	90.50	45.90

*Comment*—Marked clinical improvement followed sodium tetrathionate therapy in a patient with infected gangrenous ulceration of the foot. Elsewhere cervical and lumbar sympathectomies and multiple peripheral nerve resections were performed over a ten-year period without affecting the course of the disease. Following his refusal of amputation the patient came under our care. After clinical improvement occurred and no treatment had been given for four months, arterial blood oxygen studies

were carried out. The initial percentage of oxygen saturation was unusually low but increased to normal after intravenous therapy.

CASE 7.—Mr. B., aged 27 years, a Lithuanian gentile electrician, was admitted to the hospital March 13, 1936, having suffered for one year with thromboangiitis obliterans of both lower extremities. There were infected gangrenous ulcerations of the left first, fourth, and fifth toes and adjacent portion of the foot. He was a heavy cigarette smoker.



A.

Figs 5 A and B.—Clinical recovery from infected gangrenous ulceration of right foot followed treatment. Previously, cervical and lumbar sympathectomies and multiple peripheral nerve operations had been performed elsewhere (Case 6). A. Before treatment. B. After treatment.

Daily injections of sodium thiosulfate were followed by relief of pain within six weeks, but spontaneous amputation of the three gangrenous toes and healing of the wound did not occur for three months. Because of the infection, pavaex treatments were used cautiously and infrequently. Four months later he returned to work.

Almost two years later on Aug. 31, 1938, he was readmitted with infection of the remaining toes of the left foot. Injections of sodium tetrathionate and pavaex treatments resulted in sufficient improvement to permit his discharge Oct. 12, 1938. He then resumed heavy smoking, but his condition continued to improve and he returned to work in January, 1939. In February, his foot again gave him trouble and he was refused further treatment because he would not stop smoking. Amputation of the leg was then performed elsewhere and he remained in the hospital for nine months without the wound completely healing.



Fig. 5B—See opposite page for legend

In May, 1940, he returned to us for a checkup and was told again to stop smoking. On Dec. 26, 1940, he returned with a marked involvement of both hands and the right (trailing) foot, but no infection or gangrene. Clinical improvement followed biweekly injections of sodium tetrathionate for three weeks. The initial



oxygen saturation of the arterial blood (femoral artery) of 81 per cent was increased to 92.4 per cent following the first injection. The clinical improvement was accompanied by an increase in the sedimentation time from one hour to six hours (Linzenmier method).

*Comment.*—Complete recovery followed two serious attacks of infected gangrenous ulcerations of the foot. With the third recurrence, amputation was performed elsewhere. Two years later both hands and the remaining foot became involved and the patient returned to us for treatment. Marked clinical improvement was accompanied by a normal percentage of oxygen saturation of the arterial blood and by normal sedimentation time.



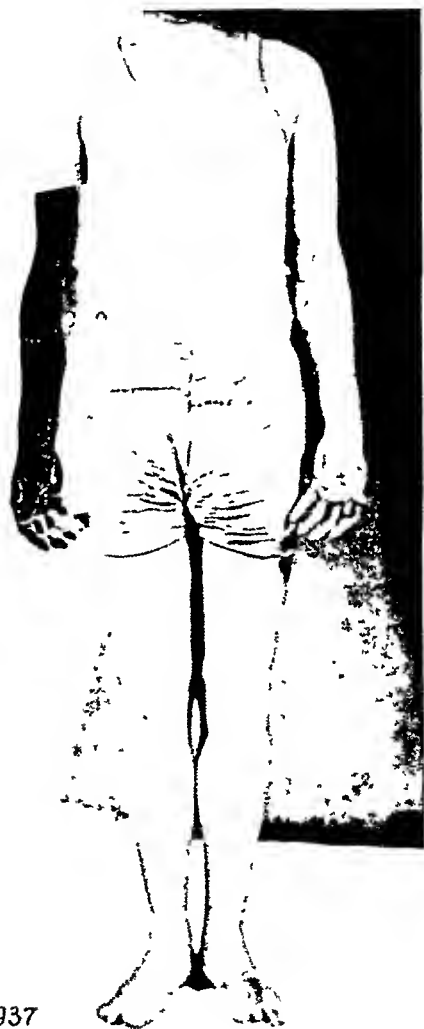
A.

Figs. 6 A and B.—Clinical recovery from two serious attacks of infected gangrenous ulcerations of foot followed treatment (Case 7). Amputation was performed elsewhere because of a third recurrence. Recently the patient returned to us for treatment with both hands and the remaining foot involved. A. Before treatment. B. After treatment.

CASE 8.—Mr. N., aged 35 years, a gentle automobile mechanic, suffered with progressively severe symptoms of thromboangiitis obliterans for eight months prior to the development of gangrenous ulcerations of the second, third, and fourth toes.

He was admitted to a hospital elsewhere where he refused amputation and was discharged.

He was admitted to the Presbyterian Hospital on April 26, 1937, with a foul-smelling, moist gangrene of the three lateral toes and a patch on the second toe of the right foot. The distal third of the dorsum of the foot was purplish red. Arterial pulsations were absent and the oscillometric index was 0.3 unit at the right ankle and 1.5 units on the left ankle.



Jan. 16, 1937

FIG. CB—See opposite page for legend

Daily injections of sodium tetrathionate were continued for one week when he was discharged from the hospital. He then continued lawfully injections and pavyex treatment as an ambulatory patient. Spontaneous amputation of the lateral three toes was followed by rapid healing of the wound. Within three months after treatment was started he returned to his work as a taxicab driver. He has continued in

oxygen saturation of the arterial blood (femoral artery) of 81 per cent was increased to 92.4 per cent following the first injection. The clinical improvement was accompanied by an increase in the sedimentation time from one hour to six hours (Linzenmeyer method).

*Comment.*—Complete recovery followed two serious attacks of infected gangrenous ulcerations of the foot. With the third recurrence, amputation was performed elsewhere. Two years later both hands and the remaining foot became involved and the patient returned to us for treatment. Marked clinical improvement was accompanied by a normal percentage of oxygen saturation of the arterial blood and by normal sedimentation time.



A.

Figs. 6 A and B—Clinical recovery from two serious attacks of infected gangrenous ulcerations of foot followed treatment (Case 7). Amputation was performed elsewhere because of a third recurrence. Recently the patient returned to us for treatment with both hands and the remaining foot involved. A Before treatment. B After treatment.

CASE 8.—Mr. N., aged 35 years, a gentle automobile mechanic, suffered with progressively severe symptoms of thromboangitis obliterans for eight months prior to the development of gangrenous ulcerations of the second, third, and fourth toes.

H<sub>2</sub>O)\* which we found to be slower in action but more prolonged in its effect than sodium thiosulfate.<sup>14</sup> The tetrathionate is not as rapidly eliminated in the urine as free sulfate as is the thiosulfate.

In acute cases when the immediate effect of the medication is desirable, we alternate daily injections of the thiosulfate with the tetrathionate. As the acute stage subsides we continue periodic biweekly or weekly injections of the sodium tetrathionate solution. The usual intravenous dosage which we have been using is 1 Gm. of the sodium thiosulfate and 0.4 or 0.6 Gm. of the sodium tetrathionate dissolved in 10 c.c. of sterile distilled water. Transitory reactions may occur with either drug, but as a rule they are relieved by drinking a glass of water. We have observed no serious reaction in almost 8,000 injections. The appearance of the blood and an occasional sedimentation test are usually sufficient evidence as to the course of the disease.

Pavax treatments are used for deficient circulation due to thrombotic occlusion of the peripheral arteries. These treatments, competently and adequately given, are beneficial in improving the peripheral circulation. In completely recovered patients all treatment may be discontinued, but when smoking has been resumed, periodic injections should be continued.

#### COMMENT

The clinical results in the treatment of more than sixty patients with thromboangitis obliterans have been most encouraging, especially in view of the heretofore poor prognosis of the disease.<sup>21</sup> We have observed numerous recurrences, but in every case smoking had been resumed and it was possible that the treatment had been inadequate or prematurely discontinued. In the past seven years, six patients had minor surgical procedures and one required major amputation because of extension of serious secondary infection. Another patient after a third recurrence of the disease had a major amputation elsewhere, but he returned to us two years later with both hands and the remaining foot involved. Neither amputation nor sympathetic nerve operations had changed the course of the disease in the patients whom we have observed. Our clinical results are in sharp contrast with those of Horton and Brown<sup>22</sup> who reported the eventual loss of one or more limbs in 20 to 30 per cent of the patients and who, like Homans<sup>2</sup> and de Takats and Reynolds<sup>23</sup> reported amputations for relief from intractable pain.

The most constant chemical blood change which we detected was a deficient oxygenation of the arterial blood in the active stage of the disease (Table I). The percentage of oxygen saturation was especially low after smoking had been curtailed or discontinued and was accompanied by low blood pressure and by a slow pulse rate. The unusually low oxygen capacity in some acute cases occurred after heavy smoking. Some patients with thromboangitis obliterans had erythrocyte counts

\* Sodium tetrathionate, U. S. P., is prepared for us experimentally and supplied by C. D. Searl & Co., Chicago.

excellent health (four years), but at his own request he still is receiving bimonthly injections of sodium tetrathionate. A recent arterial blood oxygen analysis was normal:

	OXYGEN		CARBON-DIOXIDE	
	CAPACITY VOLUMES	SATURATION %	CONTENT VOLUMES	%
Arterial blood				
Jan. 23, 1941: Complete clinical recovery				
Before injection	21.50	92.60	43.60	
After 0.6 Gm. sodium tetrathionate	21.50	93.30	42.50	

*Comment.*—Rapid and complete recovery of a patient with infected gangrenous ulcerations and thromboangiitis obliterans followed treatment with sodium tetrathionate. The oxygen capacity and oxygen saturation of the arterial blood is now normal and he is enjoying excellent health.



Fig 7.—Rapid and complete clinical recovery (four years) from infected gangrenous ulceration of foot, followed intravenous sodium tetrathionate and pavaex treatments (Case 8).

*Method of Investigation.*—Methods and procedures were the same as described in our previous publications.<sup>13, 14, 18, 19</sup> Except where indicated, arterial blood was obtained from the right radial artery.

*Method of Treatment.*—Prior to 1937, only sodium thiosulfate ( $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ ) was available for treatment of the pathologic blood condition. Since then we have had prepared sodium tetrathionate ( $\text{Na}_2\text{S}_4\text{O}_6$ ).

# SURGERY

VOL. 11

FEBRUARY, 1942

No. 2

## Original Communications

### MYELOSCOPY: INTRASPINAL ENDOSCOPY

J. LAWRENCE POOL, M.D., NEW YORK, N. Y.

FOUR years ago, the principle of intraspinal endoscopy was adapted to the diagnosis of lesions affecting the cauda equina and lowermost spinal cord. Since that time, nearly 400 "myeloscopic" examinations have been carried out.

The instrument devised for the purpose, a myeloscope,<sup>1, 2</sup> may be introduced between any of the lumbar spinous processes in much the same manner as an ordinary lumbar puncture needle. No known trauma to nerve roots has ensued.

The abnormal conditions recognizable by myeloscopy include varicose vessels; arachnoid adhesions of post-traumatic or postinflammatory origin; neoplasms; the presence of inflamed nerve roots associated with clinical neuritis; and the effects of a herniated nucleus pulposus or hypertrophied ligamentum flavum.

Myeloscopy has never before been performed on the living subject, although a similar procedure has been tried on the cadaver.<sup>3, 4</sup>

#### DESCRIPTION OF MYELOSCOPE

The myeloscope consists of several parts, of which one is an oval metal cannula (Fig. 2, A). This cannula houses a close-fitting obturator (Fig. 2, C) which facilitates insertion of the instrument. The obturator is equipped with a special guide needle (Fig. 2, B). Following introduction of the cannula, the illuminating and lens systems (Fig. 2, D and E) replace the obturator, rendering the apparatus ready for visualization (Fig. 1).

*A. Cannula.*—The cannula is an oval tubular sheath of thin metal, approximately 12 cm. in length, rated as No. 7 French (Fig. 2, A). Its distal or intraspinal portion is partially cut away on one side to allow lateral displacement of the illuminating system by the after-coming lens

Received for publication, April 9, 1941

\*D. signed by the author and made by the American Cystoscope Makers, Inc., New York, N. Y.

from 4.5 to 6 millions and colorimetric hemoglobin values of 75 to 95 per cent with abnormally low oxygen capacities. The normal relation between the oxygen capacity and the colorimetric hemoglobin value<sup>25</sup> usually returned after treatment with sodium tetrathionate or sodium thiosulfate and with clinical improvement.

Clinical improvement accompanied the increased oxygenation of the arterial blood, but from two to six weeks were usually required for complete relief from rest pains. This delay was probably due to the time required for readjustment in the systemic pathophysiologic changes which resulted from the low oxygenation of the arterial blood during the active stage of the disease. Although fairly normal oxygenation of the arterial blood may be present after the first few injections of the inorganic sulfur compounds, it seemed advisable to continue the treatment for many months. Smoking should be permanently discontinued, but it has been our experience that smoking was resumed by the large majority of these patients despite all advice and personal experience to the contrary.

#### CONCLUSIONS

The clinical results in the treatment of the biochemical blood changes in acute or active thromboangiitis obliterans with sodium tetrathionate or sodium thiosulfate and of the peripheral circulatory deficiency due to arterial thromboses with pavaex treatment have been most encouraging.

Deficient oxygenation of the arterial blood was usually present during the active stage of the disease. Following treatment for two to six weeks, the increased oxygenation of the arterial blood was accompanied by clinical improvement and in some cases by clinical recovery (five years).

The oxygenation of the arterial blood in the majority of patients with thromboangiitis obliterans which we studied was affected by smoking.

#### REFERENCES

1. Koga, G.: Treatment of Spontaneous Gangrene of the Extremities, *Deutsche Ztschr. f. Chir.* 121: 371-382, 1913.
2. McArthur, L. L.: Thromboangiitis Obliterans of Buerger: Modified Koga Treatment, *S. Clin., Chicago* 1: 499-503, 1917.
3. Silbert, S.: Treatment of Thromboangiitis Obliterans, *J. A. M. A.* 86: 1759-1761, 1926.
4. Silbert, S.: Thromboangiitis Obliterans: Results of Treatment With Hypertonic Salt Solution, *J. A. M. A.* 94: 1730-1733, 1930.
5. Silbert, S.: Thromboangiitis Obliterans, *Surg., Gynec. & Obst.* 61: 214-222, 1935.
6. Steele, W. A.: Sodium Citrate Treatment in Thromboangiitis Obliterans, *J. A. M. A.* 76: 429-431, 1921.
7. Meyer, W.: Conservative Treatment of Gangrene of the Extremities Due to Thromboangiitis Obliterans, *Ann. Surg.* 63: 280-296, 1916.
8. Rabinowitz, H. M.: Thromboangiitis Obliterans: Newer Concepts on the Physiopathology and Treatment, *Am. J. Surg.* 21: 260-271, 1933.
9. Rabinowitz, H. M.: The Use of Sodium Iodide Thiosulfate in the Treatment of Thromboangiitis Obliterans, *J. Chem.* 13: 1-4, 1936.
10. Rabinowitz, H. M., and Kahn, J.: Relationship of Phospholipin Metabolism to Thromboangiitis Obliterans and Its Treatment, *Am. J. Surg.* 31: 329-339, 1936.

cannula. The needle is provided with a standard adaptor to which a spinal fluid manometer or syringe may be fitted.

*C. Illumination.*—The illuminating system consists of a small tubular carrier (Fig. 2, *D*) through which a wire runs to the miniature light socket at its tip. The socket is eccentrically placed so that when displaced through the lateral hiatus of the cannula tip, the light bulb lies outside the cannula. The proximal end of the light carrier terminates

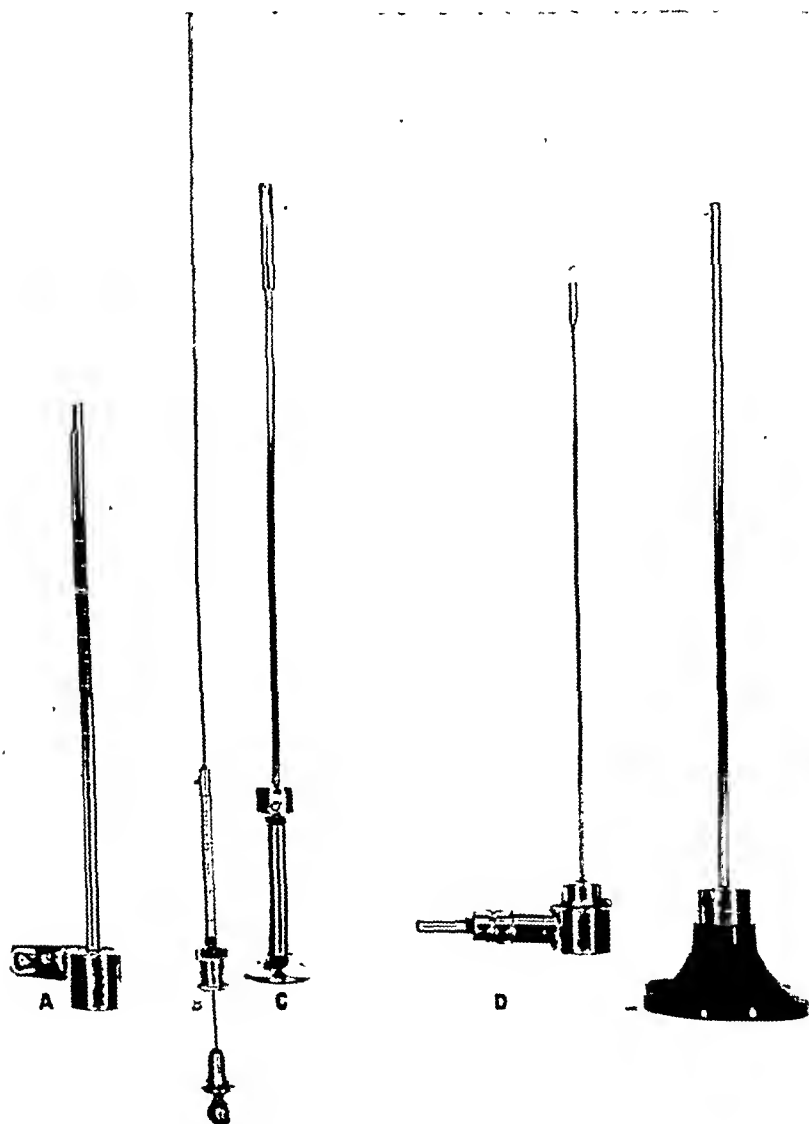


Fig 2 —A. Cannula. B. Guide needle (stylet partly withdrawn). C. Obturator. D. Lighting system. E. Lens system with eyepiece.



system. This arrangement affords material reduction in the diameter of the cannula. The external end of the cannula is equipped with an adaptor to receive the obturator or the lighting system. The adaptor is provided with a right-angle stopcock in which any standard syringe may be fitted for purposes of irrigation, introduction of oxygen, or collection of cerebrospinal fluid. Along the side of the cannula is a millimeter scale to facilitate accurate insertion of the instrument.

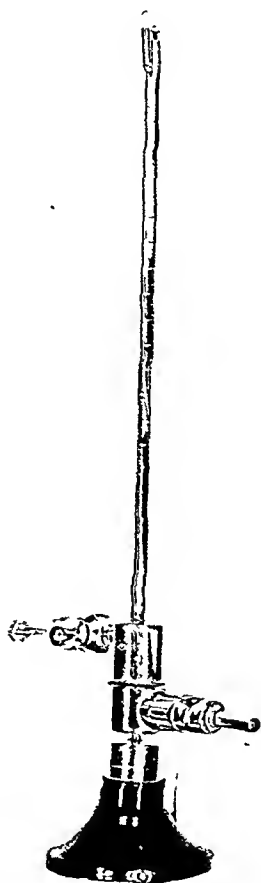


Fig. 1.—Myeloscope assembled for visualization.

**B. Obturator and Guide Needle.**—The obturator consists of a rigid metal tube which closely fits the lumen of the cannula (Fig. 2, C). Its tip, tapered to a point, extends approximately 1.6 mm. beyond the end of the cannula. Through the core of the obturator runs a No. 19 hollow “guide” needle (Fig. 2, B), which may be advanced well ahead of the obturator tip. The needle is provided with a stylet. On the handle of the needle there is a millimeter scale, corresponding to that on the

latter may be used. The sitting position greatly facilitates midline insertion of the instrument, one of the most important factors of a successful myeloscopic examination. The greater hydrostatic distention of the arachnoid and dural envelopes in the sitting posture also facilitates introduction of the instrument into the subarachnoid space. Myeloscopy should not be attempted within four or five days after a lumbar puncture, as the postlumbar puncture escape of cerebrospinal fluid into the epidural space renders myeloscopy difficult.

When the patient has been prepared as described, a small vertical incision is made in the skin at the point of the proposed puncture with a No. 11 scalpel blade. This incision, not more than 2 to 3 mm. in length, should be continued through skin, subcutaneous tissue, and interspinous ligament for a total depth of 1 to 1.5 cm. in order to establish the proper *midline* pathway for insertion of the myeloscope.

Insertion is accomplished by advancing the cannula (Fig. 2, *A*), which has been previously fitted with the obturator (Fig. 2, *C*) and guide needle (Fig. 2, *B*), along the scalpel tract and then 1 to 2 cm. farther, so that the tip of the instrument comes to rest about two-thirds the distance from skin to dura mater (Fig. 3*A*). The guide needle (Fig. 2, *B*) is now unlocked from its "neutral" position (indicated by the zero mark on its handle), and advanced ahead of the resting cannula until the dura mater and arachnoid membrane are penetrated (Fig. 3*B*). In doing this, two points of minor resistance are generally appreciated, one being caused by passage of the needle point through the ligamentum flavum, and the other by its passage through the dura mater. The stylet is then removed, whereupon cerebrospinal fluid flows out the needle. Manometric studies, if desired, should be carried out at this stage and specimens of cerebrospinal fluid obtained.

The precise distance from obturator tip to the subarachnoid space is now determined, by noting the distance the guide needle has been advanced. This distance is read from the millimeter calibration on the handle of the needle. The needle must now be restored to and locked in its original neutral position. The whole instrument (cannula with obturator and needle) is then advanced the required distance, by reference to the millimeter scale on the shaft of the cannula. The tip of the obturator should now have penetrated the dura mater and arachnoid, leaving the tip of the cannula just outside the dura (Fig. 3*C*).

The position of the instrument should be checked by withdrawing the stylet or the entire guide needle, where upon cerebrospinal fluid should flow freely. If no fluid is obtained, it may be necessary to advance the instrument another millimeter or two. It is helpful to realize that the penetration of the ligamentum flavum and of the dura mater can be appreciated by the sense of touch. It should also be remembered that a space-occupying lesion or deformity of the spine may prevent proper insertion of the instrument.

in a rounded plug fitted with an electrode, thus furnishing contact with battery wires. An aperture in the center of this plug receives the lens system.

*D. Lens System.*—The viewing system (Fig. 2, *E*) consists of a thin metal tube sheathing a series of lenses which provide a universal focus. The intraspinal end of the lens system terminates in a small window, while the proximal or extraspinal end has a conventional eyepiece. Two lens systems are furnished, one of which encompasses the field of vision almost directly ahead of the instrument, while the other provides approximately a right-angle view. This is the more useful.

*E. Range of Vision.*—The range of vision varies from approximately 0.5 to 2.5 cm. from the lens window, being limited by the curvature of the spine, the degree of illumination, and the nature of the pathology. Structures close to the objective are magnified, while those at a distance are diminished in size, though the entire field remains in sharp focus at all times. By rotating the eyepiece, inspection of the subarachnoid space within an arc of 360 degrees may be readily accomplished. At times it is necessary to rotate the entire instrument until satisfactory visualization is obtained. The field of vision may be further altered or enlarged by advancing or withdrawing the lens system within the cannula.

#### STERILIZATION

All except the glass-bearing parts of the instrument, including the rubber-covered battery wire, are sterilized by boiling.

The lens and lighting systems are sterilized by immersion for fifteen minutes in a solution of cystan green\* made by dissolving one tablet in a pint of warm water. The parts should be rinsed in sterile distilled water or saline solution before being used.

#### EQUIPMENT FOR MYELOSCOPY

The necessary equipment includes: myeloscope and battery; novocain solution; 2 c.c. syringe and hypodermic needle; small medicine glass for sterile saline solution (should it be required for irrigation); No. 11 scalpel blade; sterile drapes; sponges; sterile gloves.

#### TECHNIQUE OF MYELOSCOPY

The patient is arranged as for an ordinary lumbar puncture, save that the skin is prepared with iodine and alcohol over a wider area. Suitable drapes are applied, and a few drops of 1 per cent novocain injected into the skin at the site of the proposed puncture. Apprehensive patients should be given preliminary medication. It is advisable to place the patient in the sitting position, leaning well forward, instead of using the customary recumbent posture on the side, although the

\*Cystan green tablets contain a phenylmercuric salt having a high germicidal value with low toxicity, and have proved completely satisfactory for sterilizing the myeloscope. They are made by Charles Killgore, Inc., New York, N. Y., and can be supplied by the American Cystoscope Makers, Inc., New York, N. Y.

ing, which can then be enlarged by gently tilting or rocking the whole apparatus. Should wisps of epidural fat or arachnoid membrane interfere with visualization, further advance or rotation of the lens system may be necessary until the lens has either passed the obstructing tissue, or brushed it aside. On rare occasions, it may be necessary to inject 2 to 3 c.c. of warm sterile saline solution through the adaptor, to clear the field of extravasated blood from an epidural vein.

Another difficulty in visualization may be due to the nature of the underlying pathology. A neoplasm or extruded intervertebral disk, for example, may so fill the spinal canal that attempts to advance the needle result in compression of the underlying nerve roots and hence cause pain. The occurrence of pain should therefore be regarded as a point of diagnostic significance and should lead the examiner to reinsert the myeloscope at a higher or lower level.

Before withdrawing the instrument one should always remove the lens system first, so that the light bulb will drop back into the lumen of the cannula. A sterile dressing should then be taped securely over the puncture site, and the patient treated as after any lumbar puncture. It is of interest to note that the incidence of postmyeloscope headaches has been no higher than after an ordinary lumbar puncture despite the fact that considerable cerebrospinal fluid is sometimes lost.

#### APPEARANCE OF NORMAL STRUCTURES

The first tissue one ordinarily sees on advancing the lens system is epidural fat (Fig. 4A), which is loose, globular, and glistening in appearance, yellowish in color, and exhibits small blood vessels which course over and through its substance. It can hardly be mistaken for anything other than adipose tissue. Beyond the epidural fat lies the dura mater, which appears as a firm gray-white or slightly bluish, opaque membrane, vertically striated. If the myeloscope has been introduced lateral to the midline, a nerve root in its extradural course may be seen.

On passing the bulb and lens through the dura one visualizes the arachnoidea spinalis, which normally appears as a filmy, transparent membrane. The arachnoid membrane usually oscillates in harmony with the patient's respiratory excursions. The arachnoid membrane of the ventral aspect of the spinal canal has occasionally been visualized. On occasions, plaques of calcification, incorporated within the ventral portion of the arachnoid, were seen by the myeloscope and later verified at operation.

Within the arachnoid membrane lie the nerve roots of the cauda equina. Those first encountered are of course the dorsal roots, of which the smallest and most centrally situated are the sacral roots, as contrasted with the larger lumbar roots in a more lateral position. All the nerves are normally quite straight in course and free to oscillate with

With the cannula properly placed, the obturator and guide needle are removed and replaced first with the electric light carrier (Fig. 2, *D*) and finally with the lens system (Fig. 2, *E*). These two parts of the apparatus should be introduced with gentleness. Generally the electric bulb tip will pass at once through the dural and arachnoid openings made by the obturator, as will the after-coming lens system, whereupon visualization of the cauda equina may be carried out (Fig. 3*D*).

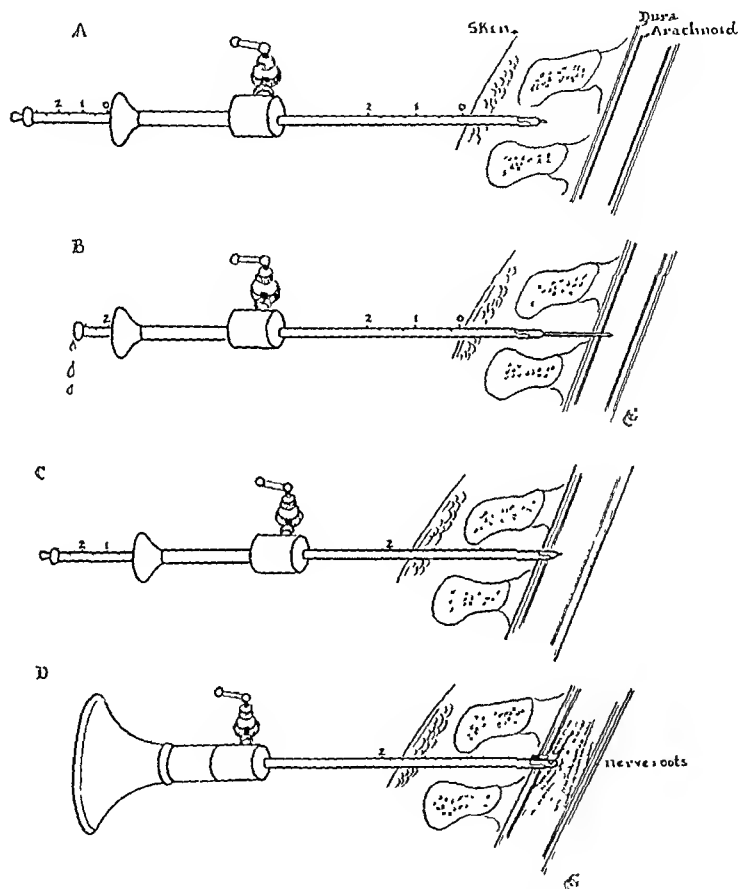


FIG. 3.—A. First step in introduction of cannula with obturator and guide needle penetrating interspinous space. B. Second step: Guide needle advanced until cerebrospinal fluid is visible; scale on handle of needle then indicates distance from obturator tip to subarachnoid space. C. Third step: With guide needle returned to original neutral position, the entire instrument is advanced the required distance. D. Final step. Obturator and guide needle are replaced by lighting and by lens systems.

It is sometimes necessary to resort to further manipulation in order to achieve a satisfactory visualization. The bulb tip, for example, may not at first penetrate the dural aperture made by the obturator. In such a case one must rotate and advance the entire apparatus under direct vision, until the bulb tip has been inserted into the dural open-

ing, which can then be enlarged by gently tilting or rocking the whole apparatus. Should wisps of epidural fat or arachnoid membrane interfere with visualization, further advance or rotation of the lens system may be necessary until the lens has either passed the obstructing tissue, or brushed it aside. On rare occasions, it may be necessary to inject 2 to 3 c.c. of warm sterile saline solution through the adaptor, to clear the field of extravasated blood from an epidural vein.

Another difficulty in visualization may be due to the nature of the underlying pathology. A neoplasm or extruded intervertebral disk, for example, may so fill the spinal canal that attempts to advance the needle result in compression of the underlying nerve roots and hence cause pain. The occurrence of pain should therefore be regarded as a point of diagnostic significance and should lead the examiner to reinsert the myeloscope at a higher or lower level.

Before withdrawing the instrument one should always remove the lens system first, so that the light bulb will drop back into the lumen of the cannula. A sterile dressing should then be taped securely over the puncture site, and the patient treated as after any lumbar puncture. It is of interest to note that the incidence of postmyelography headaches has been no higher than after an ordinary lumbar puncture despite the fact that considerable cerebrospinal fluid is sometimes lost.

#### APPEARANCE OF NORMAL STRUCTURES

The first tissue one ordinarily sees on advancing the lens system is epidural fat (Fig. 4A), which is loose, globular, and glistening in appearance, yellowish in color, and exhibits small blood vessels which course over and through its substance. It can hardly be mistaken for anything other than adipose tissue. Beyond the epidural fat lies the dura mater, which appears as a firm gray-white or slightly bluish, opaque membrane, vertically striated. If the myeloscope has been introduced lateral to the midline, a nerve root in its extradural course may be seen.

On passing the bulb and lens through the dura one visualizes the arachnoidea spinalis, which normally appears as a filmy, transparent membrane. The arachnoid membrane usually oscillates in harmony with the patient's respiratory excursions. The arachnoid membrane of the ventral aspect of the spinal canal has occasionally been visualized. On occasions, plaques<sup>5</sup> of calcification, incorporated within the ventral portion of the arachnoid, were seen by the myeloscope and later verified at operation.

Within the arachnoid membrane lie the nerve roots of the cauda equina. Those first encountered are of course the dorsal roots, of which the smallest and most centrally situated are the sacral roots, as contrasted with the larger lumbar roots in a more lateral position. All the nerves are normally quite straight in course and free to oscillate with

With the cannula properly placed, the obturator and guide needle are removed and replaced first with the electric light carrier (Fig. 2, *D*) and finally with the lens system (Fig. 2, *E*). These two parts of the apparatus should be introduced with gentleness. Generally the electric bulb tip will pass at once through the dural and arachnoid openings made by the obturator, as will the after-coming lens system, whereupon visualization of the cauda equina may be carried out (Fig. 3*D*).

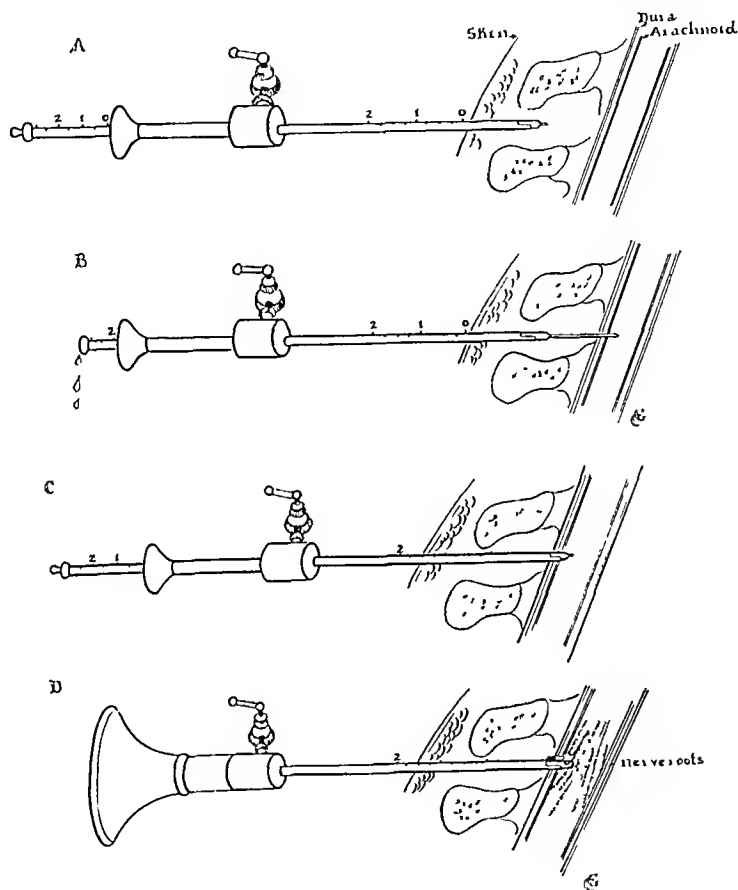


Fig. 3—A. First step guide needle penetrating advanced until cerebrospinal fluid indicates distance from guide needle returned to the required distance. Lighting and by lens systems

B. Second step. Guide needle advanced. C. Third step. With on, the entire instrument is advanced or and guide needle are replaced by

It is sometimes necessary to resort to further manipulation in order to achieve a satisfactory visualization. The bulb tip, for example, may not at first penetrate the dural aperture made by the obturator. In such a case one must rotate and advance the entire apparatus under direct vision, until the bulb tip has been inserted into the dural open-

Another example of the effects of a ventral, transverse herniated nucleus pulposus is shown in Fig. 4D. In this case the mass itself was not visible, but the overlying nerves were plainly displaced in a dorsal direction, and appeared broadened as well as discolored. On rotating the eyepiece, the same nerves appeared quite normal at a slightly higher level, as indicated in the diagram.

Unilateral extrusions of the nucleus pulposus result in compression of roots on the affected side only, so that their edges appear close together in contrast to the normal separation and oscillation of the free roots on the unaffected side. The nerves in the vicinity of such a mass often present an edematous appearance, and may have inter-rhizoid strands of arachnoid adhesions.

3. *Hypertrophied Ligamentum Flavum*.—The presence of a thickened ligament has frequently been detected by finding an unusually large epidural space, with secondary narrowing of the subarachnoid space. This condition can be appreciated in part by the difficulty of visualizing the cauda equina because of the limited intraspinal space; and in part by the sense of increased distance on passing the instrument through the ligamentum flavum (as described under the discussion of technique). It has also been possible, in a man suffering acute unilateral "sciatica," to recognize this lesion by the presence of a greatly distended, looped, root vessel, obviously due to compression of that nerve at a lower level (Fig. 4E). At operation a large wedge-shaped unilateral ligamentous mass was removed with immediate, lasting relief.

4. *Neoplastic Diseases, Primary*.—If myeloscopic examination is made directly over a large primary neoplasm such as a neurofibroma, meningioma, or ependymoma, one may be unable to visualize the tumor, owing to the cramped space, unless the examination is repeated at another level. When such a tumor is seen by close application of the lens window to the neoplasm, it appears as an amorphous lobulated, gelatinous yellow-brown tissue. Sometimes the delicate arachnoid-like membrane or capsule of the tumor, with its blood vessels, can be identified. On one occasion, when it was necessary because of pain to reinsert the myeloscope at a higher level, a discrete rounded mass was clearly distinguished, filling the spinal canal (Fig. 4F). At operation this proved to be an encapsulated neuroepithelioma, attached to the left second sacral dorsal root. The vessel on the root to which the tumor was attached appeared dilated and moderately tortuous.

*Neoplastic Diseases, Metastatic*.—Metastatic invasion of the lower spinal cord and its nerve roots from a cerebellar medulloblastoma is not infrequent. Myeloscopic examination at the level of L 1 in such a case revealed nerve roots which were so enlarged as to be tightly packed within the spinal canal; they were dull gray in color and edematous in appearance.<sup>2</sup> At autopsy several months later these findings were corroborated both macroscopically and microscopically.



the respiratory excursions of the cerebrospinal fluid. The filum terminale (Fig. 4B, central vertical structure) appears as a rather loose, small, slightly sinuous structure having a bluish tinge in contrast to the gray-white color of the nerves. Close examination of the nerve roots discloses their longitudinal fasciculi. Along the surface of each root there run one or more fairly straight blood vessels.

The flow of blood may sometimes be seen, when the lens objective is sufficiently near a root to magnify its blood vessels. In such instances, arterial circulation (red) and venous flow (bluish) can be readily distinguished, the blood coursing in opposite directions in adjacent vessels on the same root. The direction of arterial flow is caudad. Arrest and even temporary reversal of flow can be recognized when the patient coughs or strains. The administration of amyl nitrite by inhalation has produced a visible dilatation of the vessels.

#### EXAMPLES OF PATHOLOGY VISUALIZED BY MYELOSOCOPY

1. *Neuritis*.—A patient suffering from clinical neuritis of the left sciatic nerve, secondary to focal infection, was found on myeloscopy to have reddened, inflamed looking nerve roots on the left side of the cauda equina at L 4-5 (Fig. 4B). The vessels of the affected nerves were diffusely dilated in contrast to the normal nerves and vessels on the opposite side.

2. *Herniated Nucleus Pulposus*.—The effects of nerve root compression by a herniated nucleus pulposus can usually but not always be recognized by the myeloscope. A ventrally situated mass, resulting from an extruded "disk," has been seen clearly as shown in Fig. 4C. In this instance, the actual separation of nerve roots by the lesion was at once apparent, although clinical and x-ray studies had failed to reveal the site or nature of pathology. At operation, the herniated nucleus was successfully removed.

Fig 4—A Normal structures (myeloscopic appearance) showing epidural fat on each side of the field, with extradural nerve root at left. The aperture in the dura (bluish) has been exaggerated for illustration. Crossing the upper angle of the dural opening is part of the two nerve roots of the cauda equina. The space between nerve roots usually appears dark, because in shadow.

B Neuritis. Two inflamed nerve roots are seen at the left the filum terminale in the center, and two normal roots at the right. A portion of the epidural fat and underlying dura mater can be seen at the lower third of the field, while at the extreme right is a bit of the arachnoid membrane.

C. Herniation of nucleus pulposus. The transverse yellowish, ventrally situated mass represents part of an extruded intervertebral disk.

D Herniation of nucleus pulposus. Myeloscopic appearance of similar lesion to that shown in C. In this case the mass itself was not seen owing to the extreme compression of the overlying nerve roots, which were broadened and discolored, as indicated at the lower portion of the field. The same roots presented a normal appearance at a higher level.

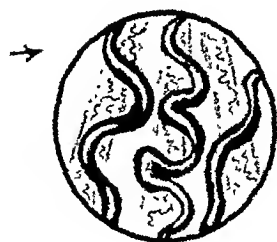
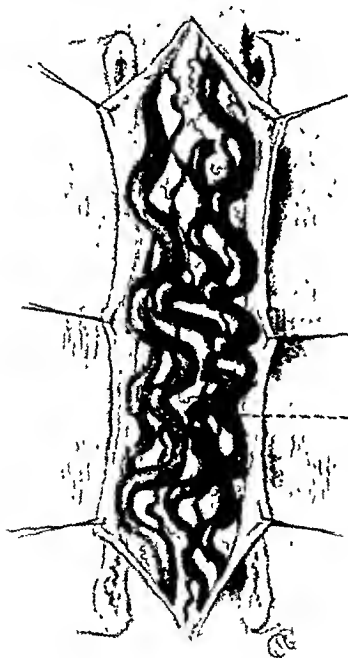
E Hypertrophied ligamentum flavum (unilateral) which caused acute unilateral sciatica due to compression of a nerve root near its foramen of exit. The lesion itself was not visualized, but the greatly dilated and tortuous blood vessel of the second root from the left indicated pressure on that nerve at a lower level (Myeloscopic findings verified at operation).

F. Neuroepithelioma of cauda equina. Myeloscopic appearance of discrete neoplasm attached to a single nerve root. Note moderate tortuosity and dilatation of blood vessel on the nerve giving rise to the tumor.

case, both arterial and venous channels may participate in the process, and the vessels in any one case may vary in degree of dilatation and corkscrew appearance.

The congenital type of varicosity generally manifests itself in young individuals during their first two decades, and is distinguished by the fact that the abnormal vessels within the lumbar canal (where they are visualized by the myeloscope) are *separate from* the nerves (Fig. 6); while the acquired type of varix, occurring in older individuals, is in general represented by dilatation and tortuosity of the vessels *on the* nerves (Fig. 5). Careful comparison of Figs. 5 and 6 will make this point clear.

Varicose vessels unattached to nerve roots. (Seen with myeloscope between L1 and L2.)



Large varicose vessels of spinal cord-T8 to T11. (Congenital type)

Fig 6—Varicose vessels of cauda equina and spinal cord of congenital type. Note that in this condition, which resembles an hemangioma, the varicose channels are separate from the nerve roots.

The congenital varicosity therefore resembles an hemangioma; whereas, the second (acquired) type of varix suggests slowly progressive dilatation of the intrinsic blood supply of spinal cord and cauda equina. In many instances, though not always, the latter type appears to have been the result of trauma. This belief is expressed because many patients suffering from this condition give a history of oft-repeated

Metastatic carcinoma involving one side of the fourth lumbar vertebra, in a patient with signs of nerve root compression at that level, has also been recognized by myeloscöpy.<sup>2</sup>

*Varicose Vessels.*—The importance of recognizing varicose vessels of the cauda equina lies in the fact that such vascular abnormalities represent a similar condition affecting the spinal cord, for the blood supply of the cauda equina is continuous with that of the spinal cord. Varices may extend the entire length of the cord, or may be confined to a few segments thereof.<sup>6</sup> Myeloscöpy is therefore indicated in patients having signs of diffuse or focal cord disease of obscure etiology, especially since x-ray treatment is often beneficial in cases of varices.

Chronic adhesive arachnoiditis and varicose vessels on nerve roots. Myeloscopic view—L<sub>1</sub> to L<sub>2</sub>.

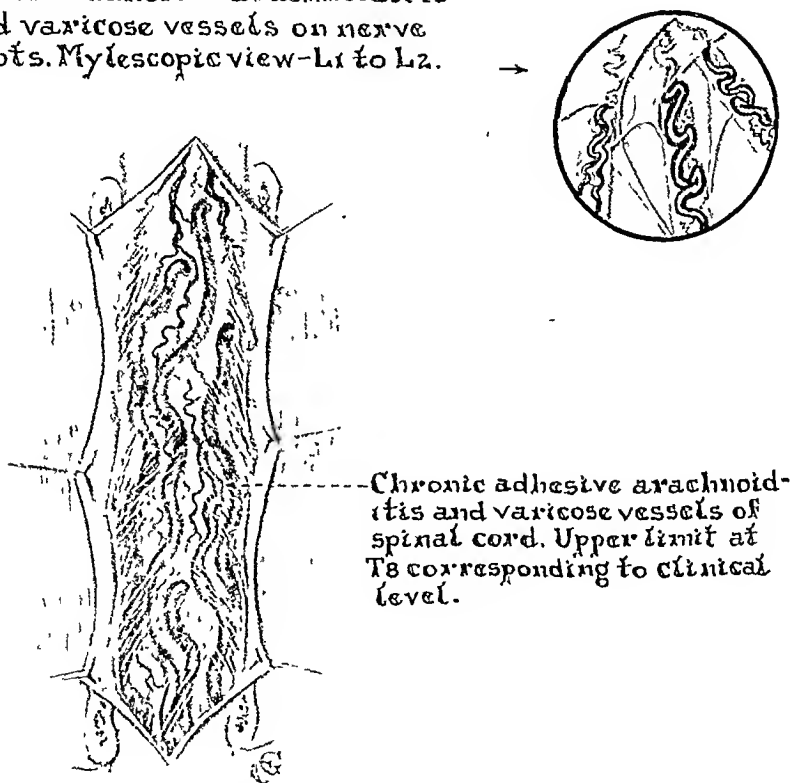


Fig. 5.—Varicose vessels of cauda equina and spinal cord with associated arachnoid adhesions: The two conditions are not necessarily coexistent. Inset shows myeloscopic appearance (upper right) while appearance at laminectomy is indicated at left. This represents the post-traumatic acquired type of varicosity, distinguished by the fact that the intrinsic vessels of the nerve roots are abnormally large and tortuous.

There appear to be two main categories of spinal varices, one congenital, the other acquired. There is sometimes an associated chronic adhesive arachnoiditis with the latter type, as indicated in Fig. 5. The characteristic features of both types of spinal varices are the enlargement and the extreme tortuosity of the involved vessels. In a given

sheets.<sup>2</sup> In certain cases the nerve roots appear glued together by the adhesive process. The arachnoid membrane itself is usually thickened and translucent, instead of being tenuous and transparent; while the nerve roots, instead of being freely movable, are firmly fixed. Patients who suffer from this process generally give a history of antecedent infection or trauma, and may have symptoms and signs of diffuse spinal cord disease.<sup>7</sup> On several occasions, patients long suspected of post-traumatic malingerer have been found by myeloscopy to harbor dense, localized adhesions on one or both sides of their cauda equina.

Operative mediation is often of value in cases of adhesive arachnoiditis, and may prevent the onset of syringomyelic cavities within the cord.<sup>7, 8</sup>

*Inflammatory Conditions of the Leptomeninges.*—When myeloscopy reveals the presence of an amorphous epidural mass, with many small blood vessels, such lesions at operation have proved to be granulomas, some associated with syphilis, others with an arrested tuberculous process, and still others of unknown etiology. Sometimes the granuloma may lie at some distance from the inflammatory reaction observed through the myeloscope.

*Lipiodosis.*—The term lipiodosis has been coined to describe the presence of subarachnoid droplets of lipiodol, following previous introduction of this oil. The lipiodol appears as tiny golden globules clinging tangentially to the nerve roots like particles of honey.

*Gas Myelography Through Myeloscope.*—Oxygen or air can be introduced into the subarachnoid space through the adapter on the side of the myeloscope after visualization has been completed. The technique differs in no way from the usual manner of performing gas myelography.

#### AFTEREFFECTS OF MYELOSCOPY

Despite the loss of from 5 to 15 c.c. of cerebrospinal fluid during myeloscopy, there has been no greater incidence of postpuncture headache than after an ordinary lumbar puncture. The reason may lie in the fact that the procedure is carried out with the patient in the upright position, so that intracranial dynamics accommodate themselves pari-passu with the outflow of spinal fluid. In this connection, it is of interest to note that the myeloscope has frequently revealed large collections of epidural fluid when an ordinary lumbar puncture has been done within the previous two to four days. This demonstrates that leakage of spinal fluid can continue for some time after an ordinary lumbar tap.<sup>9</sup> It is therefore wise to delay myeloscopic examinations for at least five days after a lumbar puncture has been done; otherwise myeloscopy may be difficult, since the dural and arachnoid envelopes will have lost their usual hydrostatic tension owing to the leak.

jarring trauma, such as from falls off a horse. This view is further substantiated by my experience in exposing the spinal cord of patients who have had some form of focal injury to the cord (such as a severe blow, or an adjacent stab wound). In such cases, varicose vessels often penetrate the substance of the cord at the level of trauma. Usually these abnormal vessels course caudally for a considerable distance, thus explaining their presence on the nerve roots of the cauda equina. There are three possible explanations of post-traumatic varices, which may act alone or in combination to produce the vascular pathology: (1) gliosis of the cord; (2) constrictive arachnoiditis around the cord; (3) traumatic insult to the vessels themselves.

Small tortuous vessels of nerve roots associated with atrophy of the spinal cord. L<sub>1</sub> to L<sub>2</sub>.

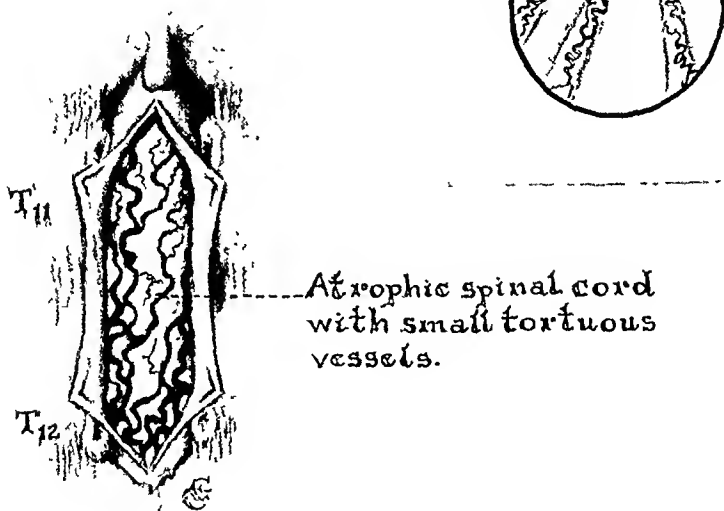


Fig. 7.—Arteriosclerosis of cauda equina and spinal cord.

Two other conditions sometimes associated with acquired variecosities are (1) arteriosclerotic atrophy of the cord (Fig. 7) and (2) intramedullary tumor of the cord. The differential diagnosis, in the final analysis, must be made by weighing every factor in a case, including history, clinical findings, course, and laboratory aids, with special reference to manometric and total protein studies.

*Arachnoid Adhesions.*—This condition can be recognized by the presence of filmy adhesions not only between the nerve roots but also between roots and the arachnoid membrane. The adhesions often resemble cobwebs scattered irregularly among the nerves, as shown in Fig. 6. They may appear as delicate strands, or as hourglass or triangular

## FRACTURES OF THE MAXILLA

### DESCRIBING A SIMPLIFIED APPLIANCE FOR CRANIOMAXILLARY SUPPORT AND FIXATION

CARL W. WALDRON, M.D., D.D.S., AND SAMUEL G. BALKIN, M.D., D.D.S.,  
MINNEAPOLIS, MINN.

**F**RACTURES of the upper jaw are of three general types: (1) Those involving a section of the jaw to include the alveolar process alone without a severance or displacement of the remaining portions of the jaw. Such a segment may be impacted into the remaining portions of the jaw and present displacement without mobility. These forms of process fractures may be combined with the second or third type of fracture. (2) Fractures of half of the upper jaw, the remaining half of the upper jaw being intact. These unilateral fractures may or may not show considerable mobility and present various types and degrees of displacement, impaction, or over-riding. (3) Complete fracture of the major portion of the upper jaw on both sides. Occasionally in horizontal fractures a portion of one tuberosity carrying a molar tooth may remain in solid continuity with the other bones of the skull. These fractures usually show mobility and displacement. They may, however, present an open bite anteriorly with the anterior portion slightly moveable; whereas, the posterior portion, the molar region, resists upward replacement to its proper occlusal level.

In the horizontal plane the fracture lines may extend through (1) the alveolar process or root-end level; (2) the midmaxillary sinus region; (3) the malar-orbit-ethmoidal level. In this latter group, danger of intracranial complication is present, and it may be wise to delay reduction of the fractures for several days in order to guard against infection and extension to the meninges.

It must be remembered that fracture lines disregard anatomic boundaries, and therefore fractures of the upper jaw of necessity must include all of the bones of the face with the exception of the frontal bone and the mandible. Consequently, they include fractures of the malar bones, lacrimal bones, the lateral masses of the ethmoid, and parts of the sphenoid.

Frequently the displacement produces a degree of malocclusion which makes it impossible to visualize the occlusion as it was before the accident. Study casts therefore should be made of the upper and lower teeth in most cases in order to determine the degree of displacement and rotation, and to make possible a more accurate application of the methods used to correct the displacement.

It has not yet seemed expedient to perform a myeloscopic examination over the spinal cord, although it has been carried out successfully within the eisterna magna of an anesthetized dog. It may be of further interest to note that the myeloscope has been used for intraventricular visualization through trephine openings in the human skull, and that attempts are now in progress to study action currents from the nerve roots of the cauda equina, through the myeloscope.

#### SUMMARY

1. *Myeloscopy*.—Diagnostic visualization of the cauda equina through a spinal endoscope called the myeloscope. Myeloscopy is usually performed under local anesthesia with the patient in the sitting posture, and is carried out in much the same manner as an ordinary lumbar puncture. Specimens of cerebrospinal fluid may be collected, manometric studies may be done, and gas myelography may be performed, through the myeloscope. Nearly 400 myeloscopic examinations have been made during the last four years.

#### 2. *Value of Myeloscopy*.—

a. Differential diagnosis may be made between operable and inoperable lesions of the cauda equina (and lower spinal cord).

b. Post-traumatic malingering may often be ruled out by this means.

c. Many a patient can be spared lipiodol injection and even an exploratory laminectomy, by preliminary myeloscopy.

3. *Operable Conditions Diagnosed by Myeloscopy*.—Herniation of nucleus pulposus; hypertrophied ligamentum flavum; chronic adhesive arachnoiditis (post-traumatic or postinflammatory); granulomas; benign tumors; lipiodosis.

4. *Inoperable Conditions*.—Varicose vessels of various types (see text); arteriosclerosis of spinal cord; metastatic neoplasms.

#### REFERENCES

1. Pool, J. L.: Direct Visualization of Dorsal Nerve Roots of the Cauda Equina by Means of a Myeloscope, *Arch. Neurol. & Psychiat.* 39: 1308, 1938.
2. Pool, J. L.: Myeloscopy: Diagnostic Inspection of the Cauda Equina by Means of an Endoscope (Myeloscope), *Bull. Neurol. Inst. New York* 7: 178-189, 1938.
3. Burman, M. D.: Myeloscopy or the Direct Visualization of the Spinal Canal and Its Contents, *J. Bone & Joint Surg.* 13: 695, 1931.
4. Stern, E. L.: Spinascope: New Instrument for Visualizing the Spinal Canal and Its Contents, *M. Rec.* 143: 31, 1936.
5. Herren, R. Yorke: Occurrence and Distribution of Calcified Plaques in the Spinal Arachnoid in Man, *Arch. Neurol. & Psychiat.* 41: 1180, 1939.
6. Globus, J. H., and Doshay, L. J.: Venous Dilatations and Other Intraspinal Vessel Alterations, Including True Angiomata, With Signs and Symptoms of Cord Compression, *Surg., Gynec. & Obst.* 48: 345-366, 1929.
7. Elkington, J. St C.: Meningitis Serosa Circumscripta Spinalis (Spinal Arachnoiditis), *Brain* 59: 181-203, 1936.
8. Lubin, A. J.: Adhesive Spinal Arachnoiditis as a Cause of Intramedullary Cavitation: Comparison With Syringomyelia, *Arch. Neurol. & Psychiat.* 44: 409, 1940.
9. MacRobert, Russell G.: The Cause of Lumbar Puncture Headache, *J. A. M. A.* 70: 1350, 1918.

dental condition of both jaws or at least the upper jaw before fully determining the procedure to be instituted. Displaced fragments should be replaced in correct position and occlusion as accurately as possible and retained by wiring or some dental appliance. In certain impacted fractures without much displacement, it is often wise to leave the fragment in its impacted position, particularly when it is obvious that future dental treatment would necessitate the removal of the teeth in the fragment in order to make the best possible dental restoration under the circumstances.

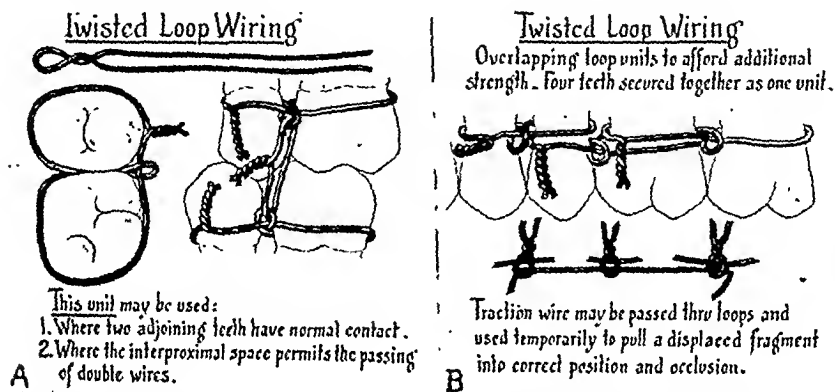


Fig. 2.—A. Twisted loop unit wiring (Ivy) is a very useful method by which the lower teeth may be secured to the upper teeth in occlusion by means of tie wires. B. Two or more loop units may be applied to overlap and secure three, four, or five adjoining teeth to provide additional strength. This is frequently necessary when strong wiring on the uninjured side of the jaw is used to elevate a fractured half of the upper jaw on the opposite side.

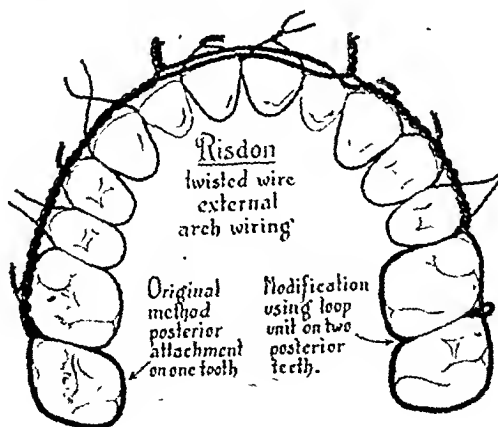


Fig. 3.—Risdon twisted wire external arch wiring is a very efficient and easily applied method of direct dental fixation to maintain two or more fragments in proper relation. Tie wires are used from the Risdon arch wire to similar arch wires or loop units on the teeth of the opposing jaw to secure the teeth in occlusion (see Fig. 1). This method has the distinct advantage that direct dental fracture fixation may be maintained after the tie wires are removed and the patient is permitted to open the mouth.



The possibility of improving a previous malocclusion must always be kept in mind. We have been able to do this in several cases during the past few years.

It should be noted that roentgenograms of fractures of the maxilla are often most unsatisfactory and one must rely upon the clinical findings and more particularly, on a study of the occlusion of the teeth in the making of the diagnosis. It is therefore unnecessary to rush patients with severe upper facial injuries to the x-ray room and submit them to the discomfort of the manipulations necessary in taking a number of films of the facial region. A limited number of carefully positioned films including dental films may be taken at a later date should it be found that complete reduction of the fracture is not accomplished by the initial treatment.

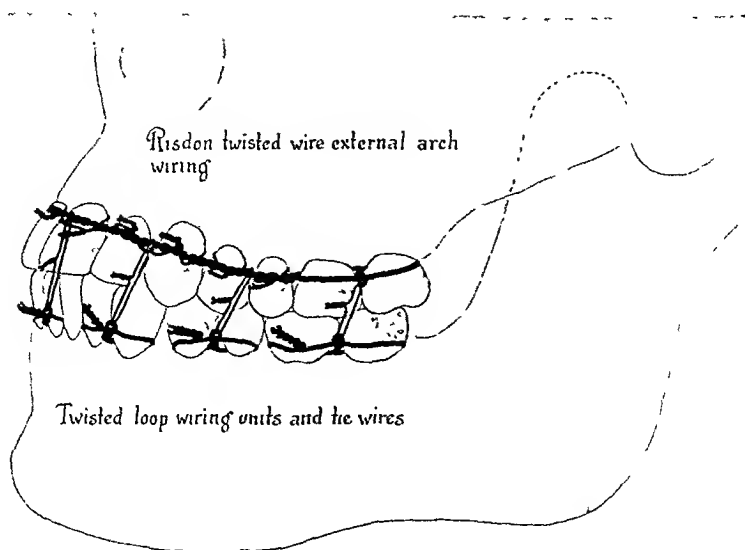


Fig. 1.—Teeth wired securely in occlusion by interdental wiring. In most cases of fractures of the upper jaw the essential treatment is the wiring of the teeth in correct occlusion after displacements have been corrected manually or by the use of diagonal tie wires or rubber-binder traction. When there is marked mobility of the entire upper jaw, this interdental wiring must be supplemented by external bandaging for a week or more.

Fractures of the alveolar process may involve the outer or inner table with the associated teeth, and the displacement may be labial, buccal, or lingual. In other cases, complete sections of the alveolar process containing the teeth may be torn loose from the body of the bone, in which case the mucoperiosteum will usually supply sufficient blood supply to maintain the vitality of the fragment.

As already noted, segments of the alveolar process may present varying degrees of mobility and may be either in a reasonably correct position or be considerably displaced. In all such fractures including the impacted fractures, it is necessary to make a careful diagnosis of the

dental condition of both jaws or at least the upper jaw before fully determining the procedure to be instituted. Displaced fragments should be replaced in correct position and occlusion as accurately as possible and retained by wiring or some dental appliance. In certain impacted fractures without much displacement, it is often wise to leave the fragment in its impacted position, particularly when it is obvious that future dental treatment would necessitate the removal of the teeth in the fragment in order to make the best possible dental restoration under the circumstances.

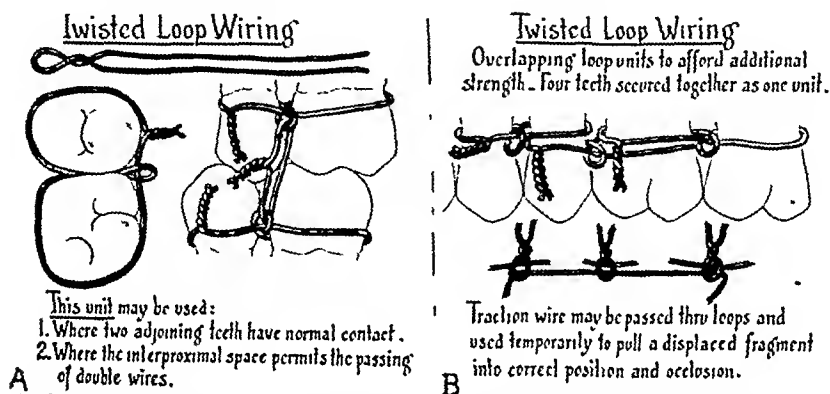


Fig. 2—A. Twisted loop unit wiring (Iv) is a very useful method by which the lower teeth may be secured to the upper teeth in occlusion by means of the wires. B. Two or more loop units may be applied to overlap and secure three, four, or five adjoining teeth to provide additional strength. This is frequently necessary when strong wiring on the uninjured side of the jaw is used to elevate a fractured half of the upper jaw on the opposite side.

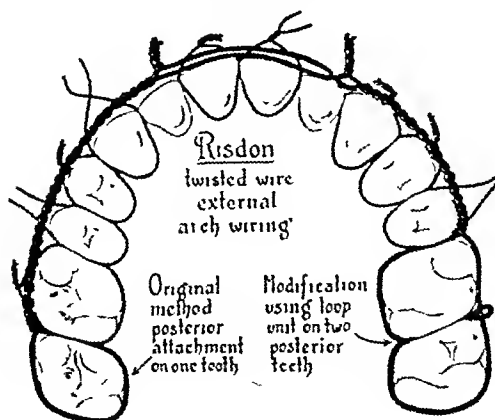


Fig. 3—Risdon twisted wire external arch wiring is a very efficient and easily applied method of direct dental fixation to maintain two or more fragments in proper position. The wires are used from the Risdon arch wire to similar arch wires or loop units on the teeth of the opposing jaw to secure the teeth in occlusion (see Fig. 1). This method has the distinct advantage that direct dental fracture fixation may be maintained after the tie wires are removed and the patient is permitted to open the mouth.

Fractions of half of the upper jaw with mobility can usually be nearly, if not completely, reduced by manipulation. In most cases, they should be maintained in correct occlusion by means of firm wiring of the teeth in occlusion on the uninjured side (Fig. 1). Two or three days of adjusting and tightening of the tie wires may be required to secure the teeth of the fractured side in good occlusion. For this purpose where considerable force is necessary, overlapping loop wiring is of great service (Fig. 2B). In addition to the wiring of the upper teeth to the lower jaw, the wiring together of the teeth on either side of the fracture may be indicated to give a finer adjustment of the ends of the fragments and to secure a more normal contact point (Fig. 3).

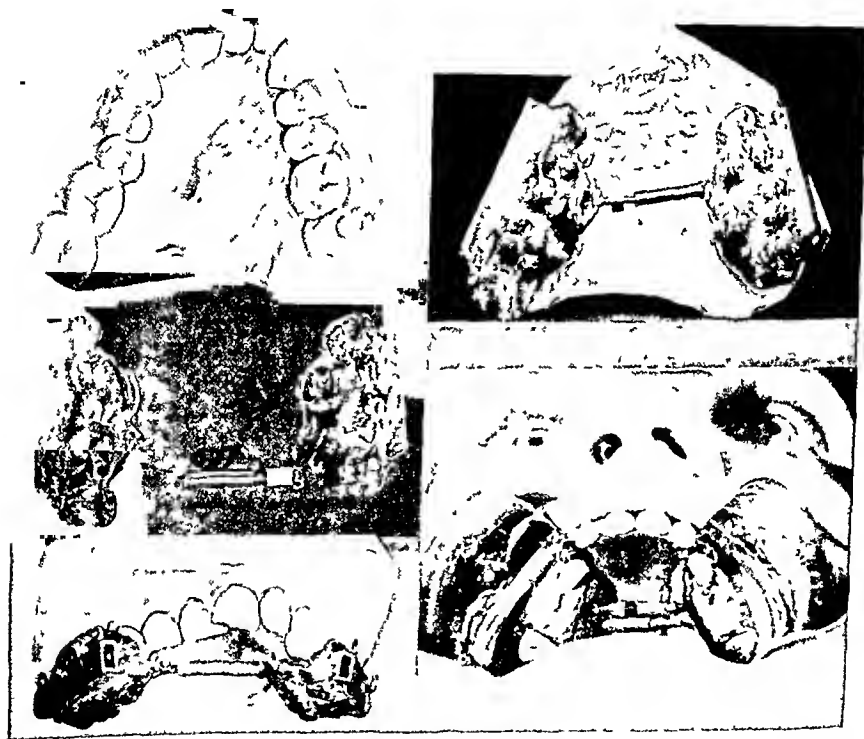


Fig 4—Jack screw splints may be used to push a fragment of the maxilla laterally to correct an over-riding at the midpalatal line. This type of splint may also be used to pull separated halves of the upper jaw together in the midline. Rectangular tubing soldered on the buccal sides of the splints may be used with extraoral arms to hold the entire upper jaw in its proper position (see Figs 7 and 8)

There may be an over-riding of the bony margins of the fragments in the midline of the palate and an attempt should be made to correct this by manipulation before the mouth is closed in occlusion. For this a jackscrew splint may be necessary (Fig. 4). At times this over-riding with a permanent ridge must be accepted. In such cases, although the teeth may be in a useful occlusion, there will likely be a slight depression with flattening of the face on the affected side. It is usually necessary to keep the teeth wired in occlusion for a period of


three or four weeks following which the mouth may be opened, and the patient allowed to partake of more solid, but yet a fairly soft, diet. The complete and solid union of fractures of the upper jaw is usually slow in cases where the initial mobility has been great. It is frequently possible to note a definite spring or slight movement of the fractured side for three or four months after the injury. In time, however, union becomes clinically quite firm, and the patient is not conscious of any spring on strong mastication. For many months the teeth on the affected side may feel prominent or numb. There will usually be recovery from these symptoms or they may become hardly noticeable.

Unilateral fractures of the upper jaw may result in separation of the two halves of the jaw at the midpalatal suture line. These may prove to be difficult to approximate by the usual methods of wiring the teeth in occlusion and at times a special appliance must be constructed across the palate to use a jack screw to pull the displaced fragment into correct relationship with the uninjured side (Fig. 4). Rubber binder traction across the palate has been employed for the same purpose.

Complete fractures of the upper jaw show a wide variety of displacements according to the direction of the lines of fracture and the horizontal levels of the severance of the jaw from the deeper structures. At times, the jaw will be found mobile and subject to correction of the occlusion with but little manipulation. In a larger number of cases, the jaw is depressed and rotated, and in some instances, the entire maxilla is driven back to contact the posterior pharyngeal wall. The malar bone may also be fractured and driven down to become impacted into the displaced maxilla in such a way that the upper jaw cannot be manipulated or otherwise brought to its correct position and occlusion until the malar bone has been pulled outward and upward to its proper level.

At times, displacement may be very marked, particularly where there is depression of the molar region with open bite anteriorly, and replacement by manipulation and wiring is impossible. In such cases, a head appliance making possible the application of craniomaxillary force is indicated.

Many types of appliances have been devised to hold the fractured maxilla in its correct position by means of plaster of Paris headcaps to which are attached straps and metal arms, or by wire sutures which pass through the tissues of the cheeks. These in turn are attached to the fractured upper jaw by means of some form of dental splint or external arch bar appliance. It is obvious that methods employing straps or wire sutures can be efficient only when a strong upward or slightly diagonal pull will hold the fractured maxilla in its correct position. The extreme violence of present-day automobile accidents may result in a great deal of comminution of the thin walls of the maxilla. In such cases, any method that depends upon vertical and



Fractions of half of the upper jaw with mobility can usually be nearly, if not completely, reduced by manipulation. In most cases, they should be maintained in correct occlusion by means of firm wiring of the teeth in occlusion on the uninjured side (Fig. 1). Two or three days of adjusting and tightening of the tie wires may be required to secure the teeth of the fractured side in good occlusion. For this purpose where considerable force is necessary, overlapping loop wiring is of great service (Fig 2B). In addition to the wiring of the upper teeth to the lower jaw, the wiring together of the teeth on either side of the fracture may be indicated to give a finer adjustment of the ends of the fragments and to secure a more normal contact point (Fig. 3).

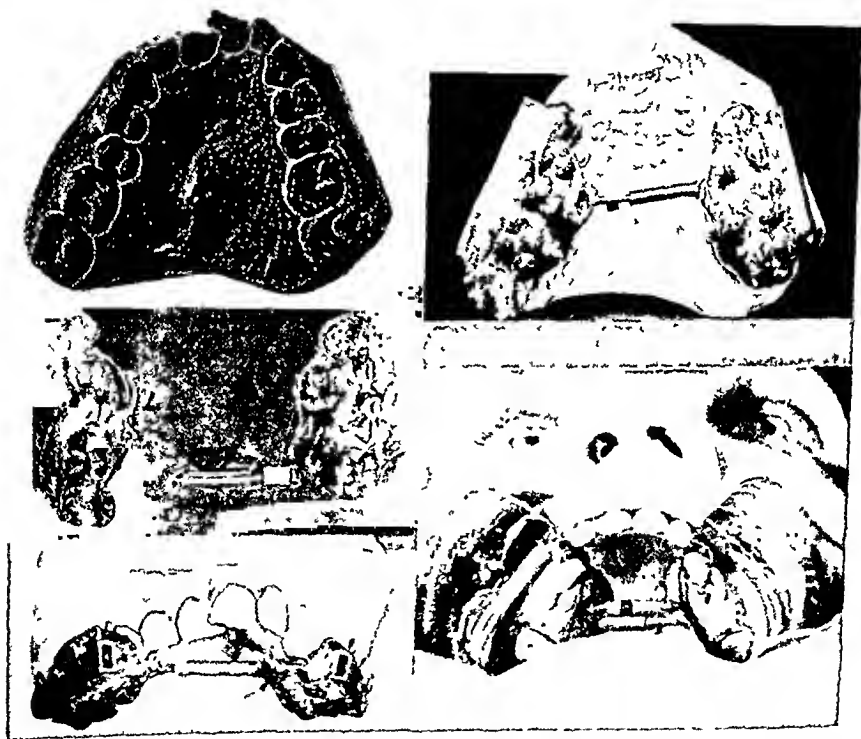


FIG. 4—Jack screw splints may be used to push a fragment of the maxilla laterally to correct an over-riding at the midpalatal line. This type of splint may also be used to pull separated halves of the upper jaw together in the midline. Rectangular tubing soldered on the buccal sides of the splints may be used with extrinsic arms to hold the entire upper jaw in its proper position (see Figs 7 and 8)

There may be an over-riding of the bony margins of the fragments in the midline of the palate and an attempt should be made to correct this by manipulation before the mouth is closed in occlusion. For this a jackscrew splint may be necessary (Fig. 4). At times this over-riding with a permanent ridge must be accepted. In such cases, although the teeth may be in a useful occlusion, there will likely be a slight depression with flattening of the face on the affected side. It is usually necessary to keep the teeth wired in occlusion for a period of

closure of the bite and probably subsequent development of traumatic changes in the temporomandibular joints. We have seen several cases of this type. Furthermore, traction straps or suspension wires do not afford adequate lateral traction or permit the application of lateral pressure upon a displaced maxilla. To overcome these faults of the appliance we began using a steel vertical extraoral arm which slips into rectangular tubing on an upper dental splint, and extends forward between the lips and then upward to be attached to a temporal plate on the headcap. This method provides efficient fixation of the jaw in all directions, but in practice it was often found difficult to bend and adjust the extraoral arm satisfactorily. Repeated removal for bending and adjustment of the arm was time-consuming and annoying to both

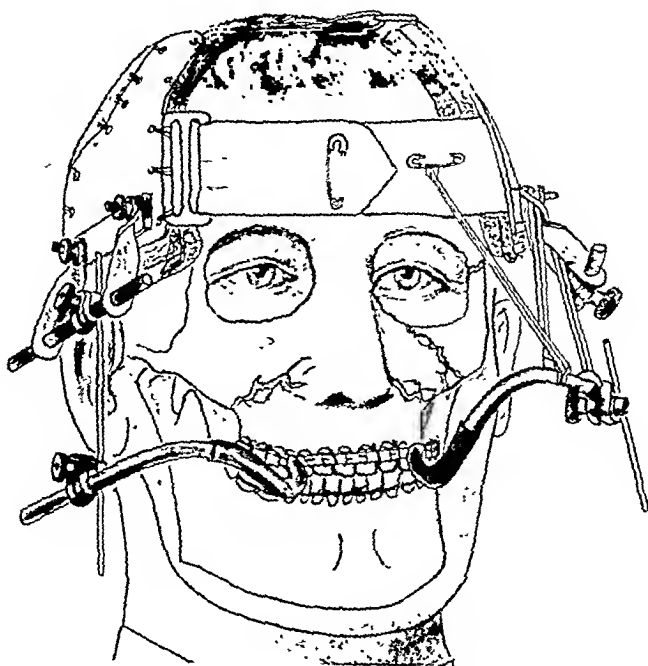


Fig. 7.—Universal upper jaw splint and headcap appliance, anterior view.

patient and surgeon. About ten years ago we discovered a type of universal joint that greatly simplified the many problems previously found so troublesome in the treatment of these cases. It permits adjustment of the displacement in all directions and planes and when tightened is most secure.\*

Instead of a vertical extraoral arm, we now use a horizontal arm, the end of which slips into the rectangular tubing on the arch bar maxillary dental splint (Fig. 5). The horizontal arm is a standard

\*This universal joint is a standard tool appliance made by the Starrett Tool Co., Chicago, Ill.; the tool sleeves of the upper unit of No. 56 Starrett surface gauge.

diagonal traction in order to immobilize the fracture may elevate the maxilla to a higher level than normal before the parts are held securely. Union of the fracture then ensues with the occlusion of the teeth at a higher horizontal level than before the accident with a resulting



Fig 5—Universal upper jaw splint consisting of an arch bar to which is soldered rectangular tubing on each side in the bicuspid molar region. Several splints of various sizes should be constructed and kept on hand. The splint is secured to the upper teeth by wiring.

## UNIVERSAL UPPER JAW SPLINT & UNIVERSAL HEAD CAP

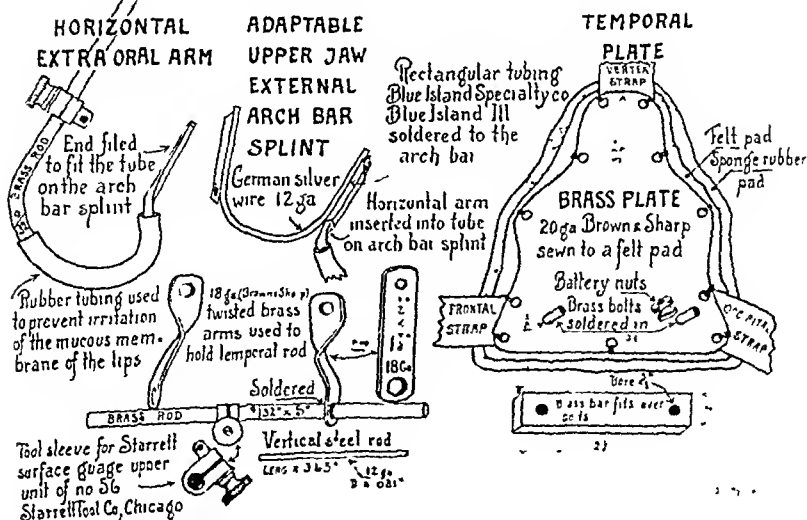


Fig 6—Detailed assembly of materials used in the construction of a universal head cap

try to maintain a proper horizontal occlusal level by wearing such an appliance for six or eight weeks.

It is often most difficult to reduce completely maxillary displacement at the first attempt and manipulations over a period of two or three days may be necessary to correct completely the displacement and restore normal occlusion. The universal joints facilitate the reduction in these difficult cases. It must be stressed that early correction of displacements is very important in the treatment of fractures of the maxilla.

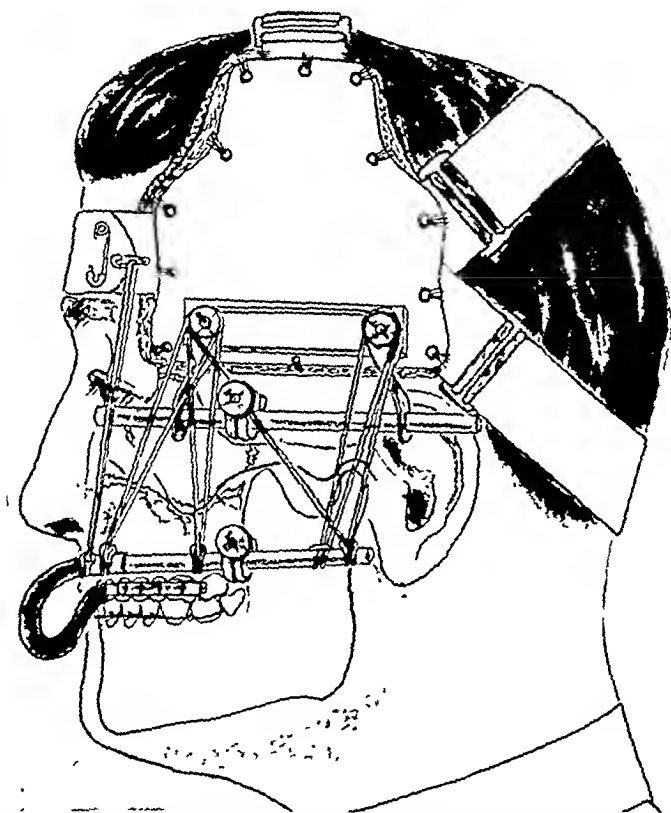


Fig. 9—Left lateral view showing the temporary use of rubber binder traction for the elevation of a depressed maxilla. Diagonal traction may be secured and an oblique or direct outward pull may be obtained from the horizontal extraoral arm to one or two vertical rods attached to the temporal rod as shown in Fig. 10.

In cases with marked lateral displacement, we have on several occasions used on one side a regular extraoral arm (Fig. 8) and on the other inserted a horizontal extraoral arm which is utilized for the attachment of rubber binders running to the temporal headplate rod or bolts (Fig. 9). By adjusting these binders and the arm, considerable pull can be exerted in an upward and outward direction. Marked resistance to replacement has succumbed to this continual force over a



brass rod  $9/32$  inch in diameter which fits the universal joint. A vertical steel rod, 12 gauge diameter, 0.081 inch, fits the universal joint and extends to a second universal joint on the brass rod of the temporal appliance to complete the fixation of the parts. We have from time to time simplified this headcap appliance. The present assembly is shown in Figs. 6 and 7. All metal materials may be obtained through hardware companies and the complete appliance may be constructed without difficulty by any good workman.

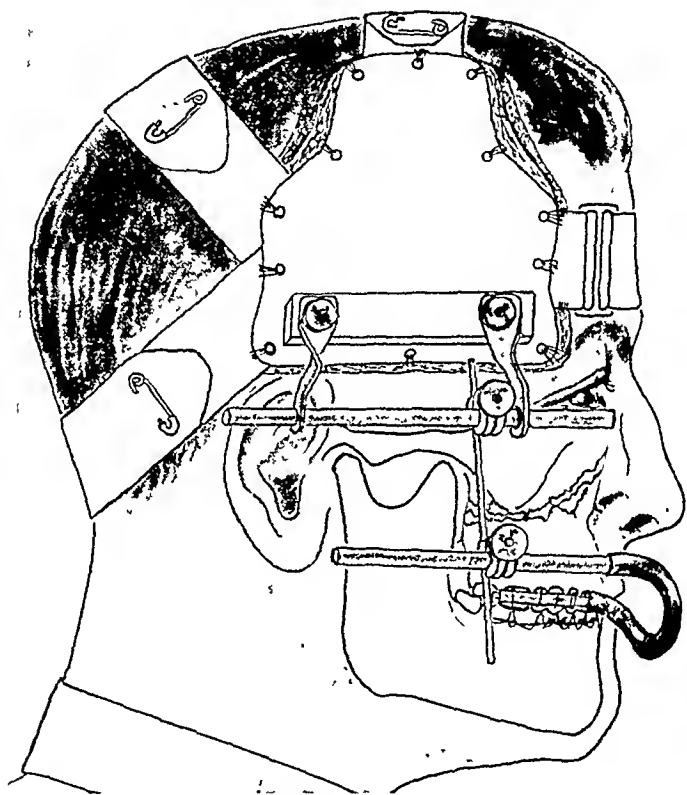


Fig. 8.—Right lateral view of appliances showing the routine immobilization of the fractured maxilla to the universal headcap.

The head appliance has been simplified and made more of the skeleton type by means of strong, adjustable cotton bands securely sewn to the temporal pads and plates (Fig. 7). These afford a more stable hold upon the occipital and frontal regions, thus overcoming the tendency of the head appliance to slip forward when considerable force is necessary to elevate and hold the fractured upper jaw. This forward slipping is an annoying and troublesome characteristic of the orthopedic plaster headcap made of stockinet, harness felt, temporal head plates, and plaster of Paris bandages which we formerly used. In markedly crushed and comminuted fractures it has been considered necessary to

period of twenty-four hours. At this time, the teeth may be wired together by the loop method of indirect dental fixation or the splint may be used further and a vertical rod attached to the horizontal arm, discontinuing the rubber binders. In practice, the emergency headcap is reinforced and made to fit more securely by means of several strips of adhesive tape or by ace bandage (Fig. 10).

Except in extremely complicated cases with loss of many teeth and lack of occluding teeth in the mandible, the head appliances may be dispensed with in a week or so and the teeth wired in occlusion in order to obtain a finer adjustment of the occlusion and a better ultimate result. If there should be a tendency for the mandible to move and displace the maxilla, additional support by bandaging from chin to vertex is necessary. This is much more desirable and comfortable than the wearing of a plaster headcap maxillary appliance for five to eight weeks as recommended by many authors. The great adaptability of the universal joints appliance makes it possible to dispense with the headcap appliance and horizontal arm at the earliest possible time. Should occasion arise, it may be quickly reapplied without difficulty. After four to six weeks have elapsed, the tie wires may be cut and the patient allowed to open the mouth and eat soft food. Very slight mobility of the maxilla may be demonstrated for several months, but in most cases, displacement does not recur.

Associated fractures of the lower jaw, particularly if multiple and badly displaced, present great problems in the successful handling of the cases. They tax the ingenuity of the surgeon, for new methods and appliances must be devised from time to time.

Fractures of the upper jaw that have united firmly in malposition produce a serious and handicapping malocclusion of the teeth. Many factors must be considered before determining the plan of treatment that should be followed. The age and condition of the patient together with the absence of several teeth or the loosening or root-end infection of a number of teeth may indicate that extraction of all of the remaining upper teeth and the construction of an upper denture to re-establish normal occlusion with the teeth of the lower jaw, is the treatment of choice. Fixed or removable dental bridgework may be indicated in some patients to secure the desired occlusion and aesthetic result.

In younger patients with a full complement of normal teeth, examination of study casts made from impressions of the upper and lower teeth may reveal that surgical refracturing of the maxilla and repositioning will restore normal occlusion and efficient mastication. The horizontal plane of the surgical refracturing should be just above the level of the floor of the nose. We have used small chisels and osteotomes for the division of the vomer, both antrobasal walls of the inferior meati of the nose, and the buccal walls of both maxillary sinuses. The posterior

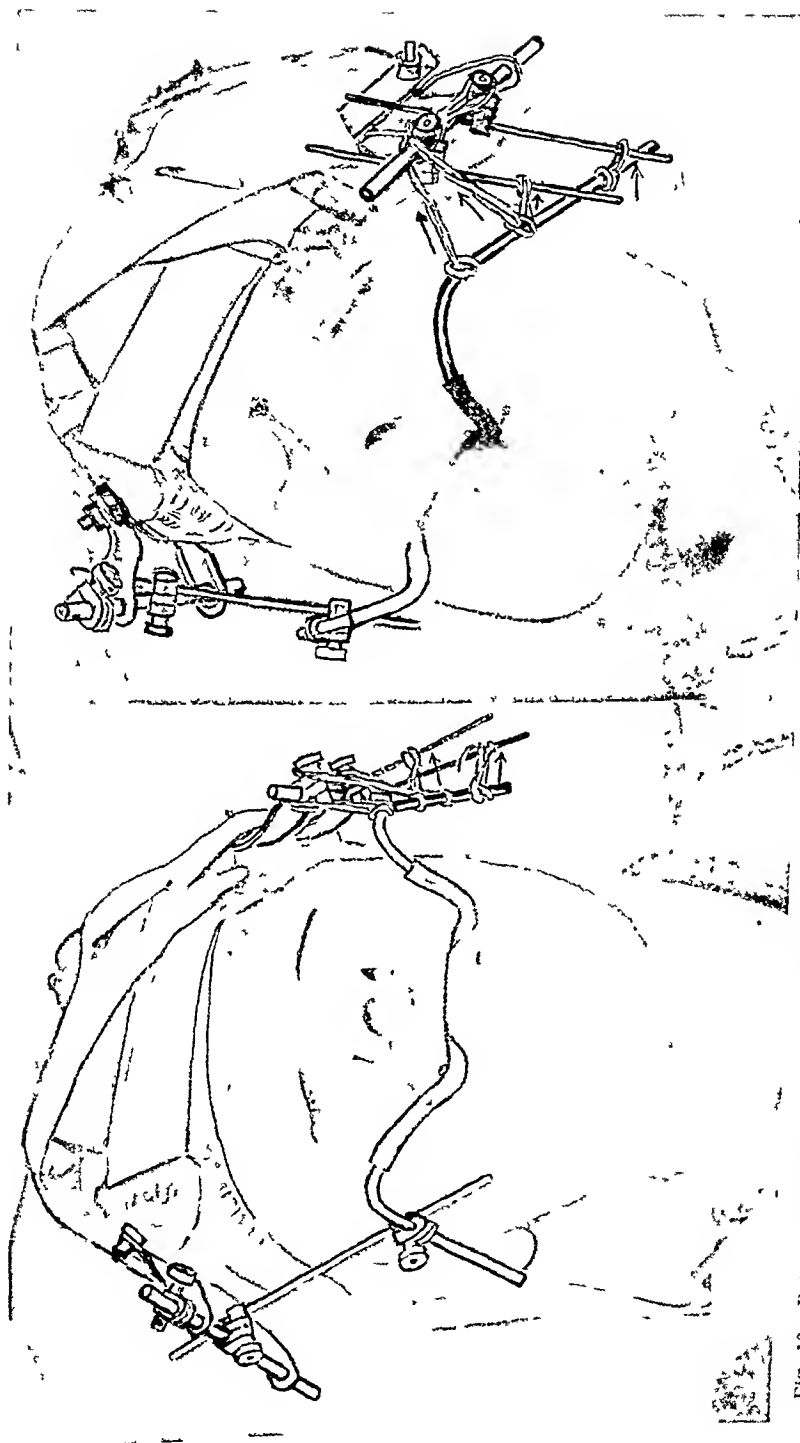


Fig 10.—Retouched photographs of patient with universal upper jaw splint and headcap appliance showing routine assembly of horizontal and vertical rods. Rubber-binder traction is used to elevate the left side of the maxilla and move the maxilla to the left.

# SOME OBSERVATIONS ON THE QUICK HIPPURIC ACID TEST IN HEPATIC FUNCTION\*

DARRELL A. CAMPBELL, M.D., ANN ARBOR, MICH.

(From the Department of Surgery, University of Michigan)

AT PRESENT it is generally considered that the conjugation of hippuric acid is at least as accurate and reliable as other liver function tests now in general use. Other authors have described in detail the technique,<sup>1</sup> the advantages and disadvantages<sup>1, 2, 6, 7</sup> and the clinical application of this test.<sup>2, 4</sup> It is the purpose of this paper to suggest that a more careful analysis should be made of the patients on whom this test is to be employed, with respect to available carbohydrate for purposes of metabolism, in order that fallacious interpretation of the degree of hepatic function may not be made.

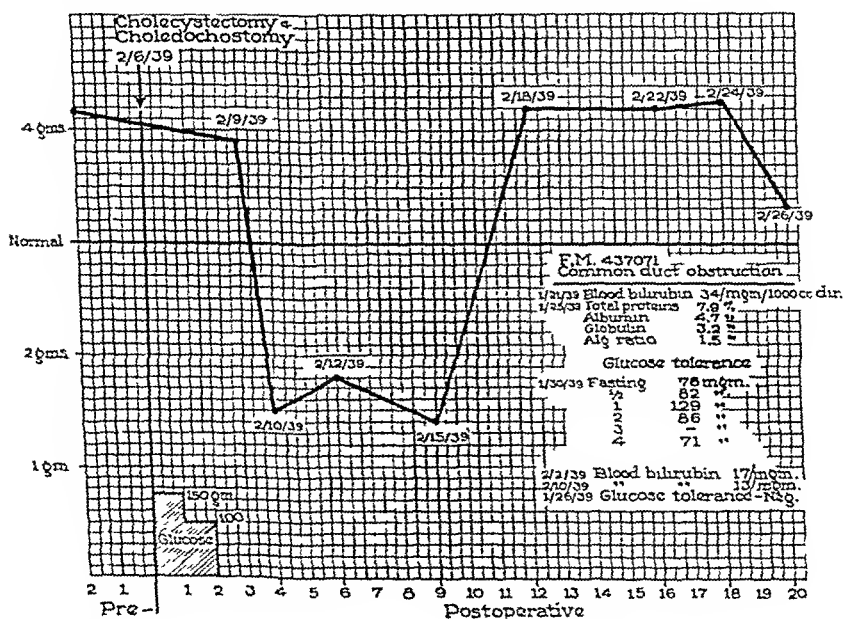


Fig. 1.—This chart demonstrates the immediate postoperative effect of supporting intravenous glucose in sustaining a normal hepatic function. The apparent depression in liver function from the fourth to ninth postoperative days was following the cessation of intravenous glucose and before the patient was able to resume a diet adequate in carbohydrate.

In this study 252 tests were done on 69 patients. In a series of patients not exhibiting clinical or laboratory evidence of liver damage, and in whom no operation was performed, uniformly normal values were obtained, confirming the work done earlier by Quick,<sup>1</sup> Vaccaro,<sup>6</sup> Boyce and McPetridge,<sup>2</sup> and others. In approximately thirty patients with

\*Aided by a grant from the James and Elizabeth Inglis Fund for Surgical Research. Received for publication, April 15, 1941.

attachments in the pterygoid region were then separated by prying the jaw loose. The maxilla was then repositioned and immobilized in the manner already described (Figs. 1, 2, 3, 5, and 7).

## REFERENCES

1. Ivy, R. H., and Curtis, L.: *Fractures of the Jaws*, Philadelphia, 1931, Lea & Febiger.
2. Seogin, C. W.: *Internat. J. Orthodontia* 14: 526, 1928.
3. Morgan, W. M.: *J. Am. Dent. A.* 21: 1736, 1934.
4. Goodsell, J. O.: *Dent. Cosmos* 83: 721, 1931.
5. Kazanjian, V.: *J. Am. Dent. A.* 14: 1607, 1927.
6. Straith, C. L.: *J. Michigan State Med. Soc.* 47: 1249, 1935.
7. Davidson, J. B., and Brown, A. M.: *Mil. Surg.* 87: 26, 1940.
8. Federspiel, M. N.: *Wisconsin M. J.* 33: 561, 1934.
9. Straith, C. L.: *J. A. M. A.* 109: 940, 1937.
10. Dingman, R. O.: *J. Am. Dent. A.* 26: 173, 1939.
11. Waldron, C. W.: *J. Lancet* 53: 351, 1933.

# SOME OBSERVATIONS ON THE QUICK HIPPURIC ACID TEST IN HEPATIC FUNCTION\*

DARRELL A. CAMPBELL, M.D., ANN ARBOR, MICH.

(From the Department of Surgery, University of Michigan)

AT PRESENT it is generally considered that the conjugation of hippuric acid is at least as accurate and reliable as other liver function tests now in general use. Other authors have described in detail the technique,<sup>1</sup> the advantages and disadvantages<sup>1, 2, 6, 7</sup> and the clinical application of this test.<sup>2, 4</sup> It is the purpose of this paper to suggest that a more careful analysis should be made of the patients on whom this test is to be employed, with respect to available carbohydrate for purposes of metabolism, in order that fallacious interpretation of the degree of hepatic function may not be made.

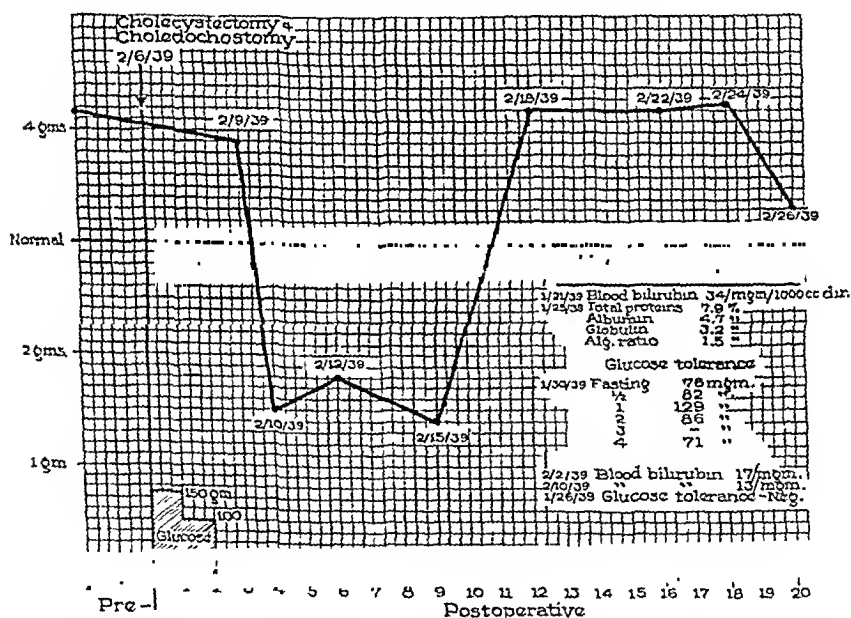


Fig 1—This chart demonstrates the immediate postoperative effect of supporting intravenous glucose in sustaining a normal hepatic function. The apparent depression in liver function from the fourth to ninth postoperative days was following the cessation of intravenous glucose and before the patient was able to resume a diet adequate in carbohydrate.

In this study 252 tests were done on 69 patients. In a series of patients not exhibiting clinical or laboratory evidence of liver damage, and in whom no operation was performed, uniformly normal values were obtained, confirming the work done earlier by Quick,<sup>1</sup> Vaccaro,<sup>6</sup> Boyce and McFetridge,<sup>7</sup> and others. In approximately thirty patients with

\*Aided by a grant from the James and Elizabeth Inglis Fund for Surgical Research. Received for publication, April 18, 1941.

H.D. 436508  
Cholelithostomy  
(No stone in common duct)

1/9/39 Blood bilirubin 44 mgm/1000cc dir.  
1/25/39 " " " 7 " " " dil."  
1/13/39 Urobilinogen Negative-all dil.

Operation  
(Cholecystectomy &  
Cholelithostomy)

1/19/39

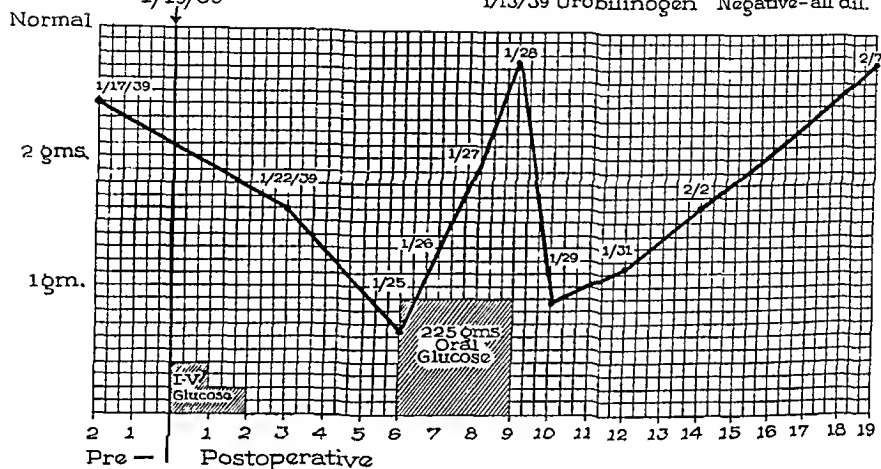


Fig. 2.—This chart demonstrates the apparent depression in hepatic function following cessation of intravenous glucose and the return to normal when large amounts of oral glucose were given. As a normal diet was resumed on the twelfth to fourteenth postoperative days, the excretion of hippuric acid again returned to normal.

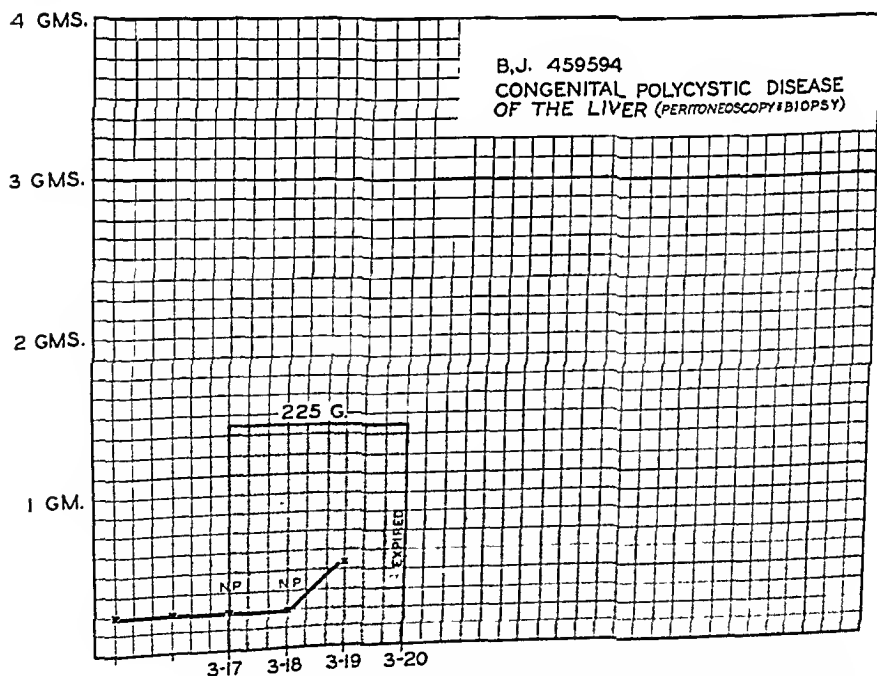


Fig. 3.—In a positively demonstrated case of severe liver damage, large amounts of carbohydrate failed to change significantly the hippuric acid excretion. N. P. No precipitate.

and without clinical evidence of biliary disease on whom some type of surgical procedure was carried out, multiple hippuric acid tests were made.

Coleman,<sup>5</sup> using the bromsulfalein test, and Boyce and McPettridge,<sup>2</sup> using the hippuric acid test, have found immediate depression in the liver function following anesthesia, and have assumed that temporary damage to the liver occurred. Boyce and McPettridge have also suggested that this depression is affected by the amount of glucose ingested prior to the test.

In this series, depression of the conjugation of hippuric acid did not occur postoperatively until after cessation of intravenous or oral glucose. At a point in the convalescence of the patient where a normal diet was tolerated (Fig. 1), or where intravenous dextrose was again employed for some untoward complication (Fig. 2), the excretion of hippuric acid again reached a normal level. Conversely, in a few patients where clinical or later autopsy evidence of severe liver damage was present (Fig. 3), no amount of intravenous or oral carbohydrate was sufficient to raise the excretion of hippuric acid to a normal level.

It may be assumed then that a liver with an insufficient amount of carbohydrate does not act as a normal liver, and does not conjugate benzoic acid and glycine in a normal manner or in normal amounts. Another less probable explanation is that in a liver low in carbohydrate, the amino-acid glycine, which ordinarily is present in adequate amounts in the body to conjugate with benzoic acid, must be used to metabolize the fats if acidosis is to be prevented, and thus an insufficient amount is left to give a normal hippuric acid value.

It is suggested then that if the hippuric acid test is to be of value in estimating hepatic function, enough carbohydrate must be furnished the patient over a sufficiently long time to make certain that the ability of the liver to conjugate benzoic acid and glycine is not impaired.

#### CONCLUSION

The use of the excretion of hippuric acid as a test of hepatic function is more reliable when the patient has had an adequate supply of carbohydrate prior to the test.

#### REFERENCES

1. Quick, A. J.: Clinical Value of the Test for Hippuric Acid in Cases of Disease of the Liver. *Arch. Int. Med.* 57: 544-557, 1936.
2. Boyce, F. P., and McPettridge, E. M.: Studies of Hepatic Function by the Quick Hippuric Acid Test. 1. Biliary and Hepatic Disease. 2. Thyroid Disease. 3. Various Surgical States. *Arch. Surg.* 37: 401-456, 1938.
3. Quick, A. J.: The Synthesis of Hippuric Acid: A New Test of Liver Function. *Am. J. M. Sc.* 185: 630-635, 1933.
4. Snell, A. M., and Plunkett, J. L.: The Hippuric Acid Test for Hepatic Function. Its Relation to Other Tests in General Use. *Am. J. Dig. Dis.* 2: 716-721, 1936.
5. Coleman, F. P.: The Effect of Anesthesia on Hepatic Function, *SURGERY* 3: 87-88, 1938.
6. Vaccaro, P. P.: The Synthesis of Hippuric Acid, *Surg., Gynec. & Obst.* 61: 36-42, 1935.
7. Yurdumun, K., and Rosenthal, P. J.: Hippuric Acid Elimination as a Test for Liver Function, *J. Lab. & Clin. Med.* 22: 1046-1053, 1937.



## POSTOPERATIVE CHOLORRHEA

REPORT OF A CASE, WITH PROFOUND PERIPHERAL CIRCULATORY COLLAPSE  
(SHOCK) DUE TO EXCESSIVE LOSS OF FLUID AND ELECTROLYTES  
THROUGH A T-TUBE

F. RAYMOND KEATING, JR.,\* M.D., MARSCELLE H. POWER, PH.D., AND  
JAMES T. PRIESTLEY, M.D., ROCHESTER, MINN.

*(From the Division of Biochemistry, the Mayo Foundation, and the Division of  
Surgery, the Mayo Clinic)*

FOSTER and his associates,<sup>5, 6</sup> and Wangenstein and others have stressed the deleterious effects of prolonged loss of bile through biliary fistulas. Less appreciated are the significance and the possible consequences of cholorrhea, which involves the loss of an abnormally large volume of bile over a short period. Clinically, this syndrome is seen as an infrequent postoperative complication of surgery on the biliary tract. Usually it occurs among patients in whom stone in the common bile duct, or occasionally, carcinomatous involvement of the biliary passages, has been associated with chronic biliary obstruction and conspicuous damage to the liver. The appearance of profuse drainage of characteristically pale, thin bile after operation on such patients has been regarded usually as evidence of hepatic failure, and death preceded by such a condition frequently has been attributed to hepatic insufficiency. It appears likely, however, that under such circumstances death often may be caused by secondary depletion of electrolytes and fluids which accompanies cholorrhea, rather than by hepatic insufficiency alone.

The paucity of references to cholorrhea in the literature is rather surprising. Apparently, the first mention of this condition was made by Sadlier, who in 1916 reported 2 cases in which excessive loss of bile postoperatively was accompanied by circulatory collapse. In the first case removal of stones from the gall bladder and common bile duct was followed postoperatively by drainage of 3,000 to 5,000 c.c. per day of remarkably thin, light-colored bile. Five days after operation profound shock ensued. Rapid improvement followed the parenteral administration of large quantities of solution of sodium chloride, but the condition of shock recurred several times, despite treatment, until the eighteenth postoperative day, when excessive discharge of bile abruptly ceased. In the second patient marked cholorrhea developed two days after surgical removal of numerous stones of the common bile duct, and severe shock occurred on the fourth postoperative day. The patient appeared to be in extremis, with ashen color and cold skin, but rallied

\*Fellow in Medicine, the Mayo Foundation.  
Received for publication, April 25, 1941.

when sodium chloride was administered parenterally. Excessive drainage of bile subsided after thirteen days. Sadlier could find no report of similar cases in the literature and conducted a survey among surgeons especially interested in the biliary tract concerning their experiences with such a complication: eight reported having encountered the condition on a number of occasions, at times with fatal issue.

Walters and Parham in 1922 pointed out that excessive drainage of bile from patients operated upon for obstructive jaundice was an ominous sign of the development of hepatic insufficiency. Their series comprised 6 cases in which death followed some type of biliary operation and 2 of the 6 patients exhibited conspicuous cholorrhea.

Greene, Walters, and Frederickson in 1930 studied the composition of the bile of 9 patients after operative relief of biliary obstruction from various causes. Three of these patients suffered from marked cholorrhea with output of bile varying in quantity to as much as 3,500 c.c. per day. The bile was notably pale and watery in quality. The concentration and total excretion of bile acids and bilirubin were abnormally and consistently low; whereas, the average content of chloride was somewhat higher than in the 6 other cases comprising the series. Greene and his co-workers suggested that in cholorrhea loss of salt was great enough to be of clinical significance and pointed out that loss of fluids on occasion could be great enough to reduce the output of urine.

In 1932 Melchior described 1 case in which profuse cholorrhea after cholecystectomy led to prostration and death twenty days after the operation. In a second case which he described recovery occurred despite a flow of bile as high as 2,000 c.c. per day. In both instances the liver had appeared to be markedly diseased at operation and the draining bile was very pale in color. The author concluded that the profuse flow in each instance must have been the result of marked damage to the liver.

Bile excreted during a period of cholorrhea contains large amounts of mineral base and the loss of electrolytes by this means may be very large. A patient mentioned by Snell lost 80 Gm. of sodium chloride and 11 liters of fluid through biliary discharge during a three-day period. Snell has observed the volume of bile to be as great as 6,000 c.c. per twenty-four hours. He wrote that the concentration of bilirubin in such bile is very low and that the concentration of bile acids is only about one-tenth of normal; whereas, the concentrations of mineral base and chloride are increased as compared to that of normal bile.

The following case is reported because it illustrates rather clearly some of the clinical and chemical consequences of this unusual condition, and, incidentally, an interesting problem in differential diagnosis.

#### REPORT OF A CASE

An Irish farmer, aged 60 years, came to the Mayo Clinic on July 7, 1940, because of weakness. He had always been dark skinned. During the preceding five

years fatigue and progressive weakness had developed and he had lost 25 pounds (11 kg.). On two occasions he had had attacks of cramping pain in the upper part of the abdomen, accompanied by nausea, vomiting, and diarrhea, followed by passage of dark urine. On one occasion he had had visible jaundice. Fourteen months before coming to the clinic his condition had been diagnosed as "Addison's disease" elsewhere, and he had spent a year in a sanatorium, where he was treated with rest and the administration of sodium chloride and cortical hormone without subjective improvement. One daughter had had tuberculosis. The family history and personal history otherwise were irrelevant.

Results of examination at the Clinic were essentially negative, except for malnutrition, pigmentation of exposed surfaces, and diffuse melanosis. The patient's blood pressure was 128 systolic and 80 diastolic, expressed in millimeters of mercury. The patient was placed on a low salt, high potassium diet, as described by Cutler and associates, to rule out the possibility of Addison's disease. Both the chemical and clinical findings obtained by this procedure were incompatible with such a diagnosis. A four-hour specimen of urine on the third day of the test contained only 27 mg. per 100 c.c. chloride.

Urinalysis disclosed a specific gravity of 1.017; the reaction was acid. Results of tests for albumin and sugar, and microscopic examination, were negative. Reaction to the flocculation test for syphilis was negative. The content of hemoglobin was 13.6 Gm. per 100 c.c., the erythrocyte count was 3,800,000 and the leucocyte count was 3,400. The value for fasting blood sugar was 103 mg. per 100 c.c. A bromsulfalein test of liver function showed retention of dye, Grade 2. The value for plasma bilirubin was 2.0 mg. per 100 c.c.; the reaction to the van den Bergh procedure was indirect. Results of roentgenograms of the thorax and stomach were negative or normal, as were those of analysis of gastric contents. A cholecystogram disclosed a nonfunctioning gall bladder with stones. It was felt these data effectively ruled out Addison's disease, and cholecystectomy was advised.

Operation was performed Oct. 17, 1940. A grossly diseased gall bladder containing stones was removed, and several stones were taken from the common bile duct which was then closed around a T-tube. Macroscopically the liver appeared to be abnormal; biopsy revealed cirrhosis of Grade 2 on the basis of 1 to 4. A decreasing blood pressure during operation was ameliorated by the transfusion of 500 c.c. of citrated blood.

After the operation the patient failed to regain strength as rapidly as expected. Ten thousand cubic centimeters of dextrose solution and physiologic solution of sodium chloride was administered during the first four days, but thereafter the parenteral administration of fluids was discontinued, since the oral intake of fluids and the volume of urine had rapidly reached satisfactory figures. The patient's appetite was extremely poor and he remained very weak.

On the day of operation 700 c.c. of bile drained from the T-tube. The quantity increased by the fourth postoperative day to 2,200 c.c., and thereafter averaged 1,500 c.c. per day. It was light and watery in quality. The total intake of fluid, output of urine, and volume of bile are shown graphically in Fig. 1. On the morning of the eighth postoperative day the patient was weak, sweating, and unable to eat. The flow of urine was scanty (70 c.c. in sixteen hours) and the urine was concentrated. By noon the patient was prostrated and presented the picture of severe peripheral circulatory collapse with rapid, shallow respiration, weak, thready pulse, marked pallor, faint heart sounds and a blood pressure of 70 mm. of mercury, systolic, and 40 mm. of mercury, diastolic. This episode was not accompanied by nausea, vomiting, diarrhea, hicough, or abdominal pain. Because of the previous suspicion of Addison's disease, and the fact that the present state bore some similarity to acute adrenal cortical insufficiency, complete studies of blood chemistry were obtained, and without waiting for the results, vigorous treat-

ment by means of the intravenous administration of dextrose solution and solution of sodium chloride and adrenal cortical extract was instituted. Spectacular improvement followed in a few hours.

Forty-eight hours later the patient's condition appeared to be entirely satisfactory, and the intravenous administration of fluids again was discontinued. Recovery continued to be slow, and although circulatory collapse did not occur again, subsequent studies in blood chemistry on the fourteenth postoperative day indicated that such a state was again imminent. The patient once more received fluids intravenously and was given adrenal cortical extract. After administration of these was discontinued three days later, 10 Gm. of sodium chloride and 5 Gm. of sodium citrate were given daily by mouth. Clamping of the T-tube was begun the fourteenth day, and despite some discomfort to the patient, the tube remained closed after the twentieth postoperative day. From the fifteenth postoperative day onward the patient improved steadily, gaining weight and strength. His subsequent convalescence was essentially uneventful.

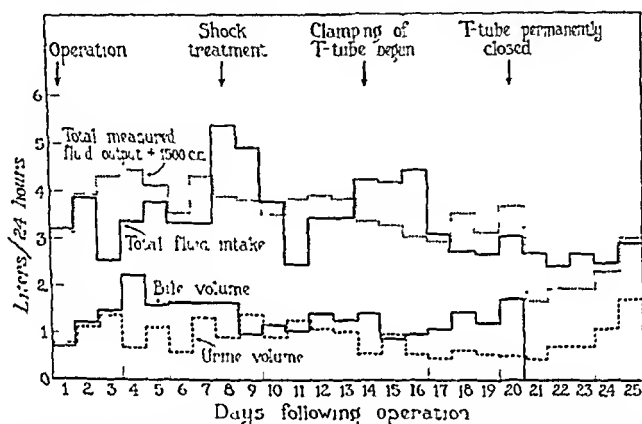


Fig. 1.—Fluid intake and output. To the measured fluid output has been added 1,500 c.c. per day to account for insensible fluid loss. The total output as estimated in this manner exceeded the intake during part of the first week postoperatively, although not by impressive amounts.

#### COMMENT

When first examined at the Clinic, this patient presented an interesting diagnostic problem. Addison's disease had been diagnosed elsewhere for him, for obvious reasons; marked asthenia, malnutrition, and pigmentation were present. However, pigmentation was limited to brown discoloration of exposed parts and a diffuse bronzing of the trunk. The creases of the palms, body folds, scars, and mucous membranes were not pigmented nor were black freckles, characteristic of adrenal disease, apparent. Adequate adrenal function was indicated by results of the salt deprivation test, and the demonstration of hepatic disease associated with cholelithiasis was felt to afford a perfectly adequate alternative explanation of all the symptoms.

When seen on the eighth postoperative day, the patient presented a picture of severe prostration and extreme peripheral circulatory collapse which again might have been mistaken for the crisis of Addison's

disease. There were a number of reasons for the belief, however, that his condition did not represent adrenal cortical insufficiency: (1) results of the salt deprivation procedure done two months earlier had been entirely satisfactory and completely negative; (2) the clinical picture differed from that of acute adrenal cortical insufficiency in the absence of vomiting, diarrhea, hiccoughs, or abdominal pain; (3) the patient had survived a long and difficult operation and six days of convalescence, a course of events most improbable for a patient suffering from untreated Addison's disease; and (4) results of chemical studies of the blood and urine differed from those encountered in Addison's disease.

Because of the previous uncertainty as to the correct diagnosis, the patient was subjected to rather intensive study during the ensuing two weeks. Samples of blood were collected under oil and centrifuged. After the hematocrit value had been determined, the plasma was removed and examined for specific gravity, and for content of sodium, potassium, chloride, total protein, nonprotein nitrogen, and urea. Twenty-four-hour samples of urine and bile were analyzed for sodium, potassium, and chloride. Determinations of the specific gravity of the plasma were made by means of the Kagan proteinometer; total protein was determined by means of a modified Kjeldahl method. Details of other chemical analytic methods employed are described elsewhere.<sup>18</sup>

*Results of Laboratory Studies.*—The laboratory data are summarized in Table I and the changes observed in the blood are represented graphically in Fig. 2. The hematocrit value, specific gravity of the plasma and plasma proteins were employed as indices of hemoconcentration. When the patient was first observed to be in circulatory collapse, all three were proportionately and markedly elevated. The cell volume as determined by the hematocrit was 62 per cent; plasma proteins were 11.0 Gm. per 100 c.c. and specific gravity of the plasma was 1.036. These values suggest a rather marked reduction in plasma volume. In a sample of blood obtained sixteen hours later these determinations were relatively normal, but six days later the figures again indicated increasing hemoconcentration despite the fact that clinical evidence of shock had not developed: the hematocrit value was 52 per cent, specific gravity of the plasma was 1.032, and plasma proteins were 9.5 Gm. per 100 c.c. With additional treatment the indices of hemoconcentration decreased and thereafter remained within normal ranges.

The first specimen of blood analyzed contained 96 mg. per 100 c.c. nonprotein nitrogen, of which 76 mg. per 100 c.c. represented urea nitrogen. That this retention of nitrogen was associated with circulatory collapse and hemoconcentration rather than any intrinsic type of renal insufficiency is shown by the rapidity with which a decrease to normal values occurred. An increase in nitrogen did not accompany the hemoconcentration which took place the thirteenth and fourteenth days

TABLE I  
SUMMARY OF LABORATORY DATA

DAYS AFTER OPERATION	PLASMA								BILE				URINE				
	Hb MAJORIT (%) (G/L)	SPECIFIC GRAVITY	TOTAL PROTEIN, MG. PER 100 C.C.	CHLORIDE, MEQ./L.	SODIUM, MEQ./L.	POTASSIUM, MEQ./L.	N. P. N, MG. PER 100 C.C.	UREA N, MG. PER 100 C.C.	VOLUME, C.C.	CHLORIDE, MG. PER 100 C.C.	SODIUM, MG. PER 100 C.C.	POTASSIUM, MG. PER 100 C.C.	VOLUME, C.C.	SPECIFIC GRAVITY	CHLORIDE, MG. PER 100 C.C.	SODIUM, MG. PER 100 C.C.	POTASSIUM, MG. PER 100 C.C.
25	39.1	1.0213	7.9	66	133	5.3	22	16	1700	7786	5476	373	400	1.018	5174	4515	758
24	38.0	1.0253	6.9	68	136		25		1150				400	1.021	3615	3600	359
23	37.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
22	37.0	1.0279	8.0	66	125	5.1	33	31	825	825	1221	277	525	1.021	3302	2177	481
21	32.7	1.0313	8.7	81	121		33	35	1320	5191			520	1.021	3105	2257	380
20	18.3	1.0300	7.8	78	120	5.2	33	36	1250				1600	1.021	166	62	219
19	15.6	1.0270	7.4	68	127	4.0	36	32	1145				1250	1.022	161	77	191
18	14.8	1.0305	7.2	69	127	3.5	38	35	960				1340	1.022	161	77	191
17	13.1	1.0355	11.0	97	128	4.2	86	76	1510				880	1.022	2561	710	796
16	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
15	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
14	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
13	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
12	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
11	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
10	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
9	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
8	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
7	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
6	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
5	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
4	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
3	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
2	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426
1	13.1	1.0256	7.0	65	130	5.2	32	23	985	1075			400	1.019	1120	532	426

disease. There were a number of reasons for the belief, however, that his condition did not represent adrenal cortical insufficiency: (1) results of the salt deprivation procedure done two months earlier had been entirely satisfactory and completely negative; (2) the clinical picture differed from that of acute adrenal cortical insufficiency in the absence of vomiting, diarrhea, hiccoughs, or abdominal pain; (3) the patient had survived a long and difficult operation and six days of convalescence, a course of events most improbable for a patient suffering from untreated Addison's disease; and (4) results of chemical studies of the blood and urine differed from those encountered in Addison's disease.

Because of the previous uncertainty as to the correct diagnosis, the patient was subjected to rather intensive study during the ensuing two weeks. Samples of blood were collected under oil and centrifuged. After the hematocrit value had been determined, the plasma was removed and examined for specific gravity, and for content of sodium, potassium, chloride, total protein, nonprotein nitrogen, and urea. Twenty-four-hour samples of urine and bile were analyzed for sodium, potassium, and chloride. Determinations of the specific gravity of the plasma were made by means of the Kagan proteinometer; total protein was determined by means of a modified Kjeldahl method. Details of other chemical analytic methods employed are described elsewhere.<sup>18</sup>

*Results of Laboratory Studies.*—The laboratory data are summarized in Table I and the changes observed in the blood are represented graphically in Fig. 2. The hematocrit value, specific gravity of the plasma and plasma proteins were employed as indices of hemoconcentration. When the patient was first observed to be in circulatory collapse, all three were proportionately and markedly elevated. The cell volume as determined by the hematocrit was 62 per cent; plasma proteins were 11.0 Gm. per 100 c.c. and specific gravity of the plasma was 1.036. These values suggest a rather marked reduction in plasma volume. In a sample of blood obtained sixteen hours later these determinations were relatively normal, but six days later the figures again indicated increasing hemoconcentration despite the fact that clinical evidence of shock had not developed: the hematocrit value was 52 per cent, specific gravity of the plasma was 1.032, and plasma proteins were 9.5 Gm. per 100 c.c. With additional treatment the indices of hemoconcentration decreased and thereafter remained within normal ranges.

The first specimen of blood analyzed contained 96 mg. per 100 c.c. nonprotein nitrogen, of which 76 mg. per 100 c.c. represented urea nitrogen. That this retention of nitrogen was associated with circulatory collapse and hemoconcentration rather than any intrinsic type of renal insufficiency is shown by the rapidity with which a decrease to normal values occurred. An increase in nitrogen did not accompany the hemoconcentration which took place the thirteenth and fourteenth days

That the kidney could adequately conserve electrolytes is shown by the fact that on such days the urinary concentration of these substances was extremely low: for chloride, 32 to 54 mg. per 100 c.c. and for sodium 8 to 12 mg. per 100 c.c. The parenteral administration of solution of sodium chloride, on the other hand, was accompanied by the usual marked increase in the excretion of both salt and water in the urine, so that an appreciable proportion of the salt thus administered probably was soon lost.

The daily output of bile was uniformly large: 1,500 to 2,000 c.c. per day during the first week, and 1,000 to 1,700 c.c. thereafter (Fig. 1). The samples of bile analyzed contained extremely high concentrations of chloride (117 to 129 meq. per liter) and were proportionately high in sodium; values for both ions far exceeded contemporary values for the same ions in the plasma (Table II). The concentration of potassium in the bile, however, was little if any higher than in the plasma. The significance of these observations is shown by the fact that on a day on which 2,000 c.c. of bile was excreted, 17 Gm. of sodium chloride was lost by this route alone.

TABLE II

COMPARISON OF ELECTROLYTE CONCENTRATION IN PLASMA, BILE, AND URINE\*

DAY AFTER OPERATION	CHLORIDE			SODIUM			POTASSIUM		
	PLASMA	BILE	URINE	PLASMA	BILE	URINE	PLASMA	BILE	URINE
	MILLIEQUIVALENTS PER LITER								
14	81	117	9	121	140	5	4.3	5.4	11.6
20	99	129	210	137	146	262	5.2	5.6	18.4

\*First day noted (fourteenth) is one on which no extra salt was administered, and a state of relative depletion of salt existed. Second day noted (twentieth) is one on which an excess of salt existed.

Comparatively little information is available concerning the electrolyte content of apparently normal bile which is drained externally. The recent monograph by Sobotka summarized most of the published data on this subject. Tsehopp (cited by Sobotka) found in normal fistula bile 96 meq. of chloride and 4.9 meq. of potassium per liter. Greene and his co-workers found that bile excreted by their patients contained a concentration of chloride varying from about 90 to 130 meq., but averaging about 110 meq. per liter, figures in many instances above normal plasma levels. Accurate data for the sodium content of normal human bile are not available, but Rheinhold and Wilson found that apparently normal bile drained from an external fistula in dogs contained an average of 174 meq. of sodium as compared to values for sodium in the plasma of 148 meq. per liter in the same animals.

*Fluid and Salt Balance.*—The figures for intake of fluids as compared to those for the total output of fluids appeared to be satisfactory on the patient's chart. If, however, an increment of 1,500 c.c. per day is added to the measured output to account for insensible loss of water, as suggested by Collier and Maddock,<sup>2,3</sup> the loss of fluids during the



after operation, indicating that impairment of circulation of a degree sufficient to affect renal function had not occurred on the second occasion.

Study of the plasma electrolytes revealed equally profound alterations. The first sample of blood contained 76.4 meq. per liter of chloride; whereas, the plasma sodium was reduced proportionately only about one-half as much as the chloride (128.2 meq. per liter). The figure for plasma potassium, 16.9 mg. per 100 c.c., is at the lower limit of normal and is of interest chiefly because it indicates, contrary to the inference of Scudder and others, that the classic picture of shock and hemoconcentration may occur without associated hyperpotassemia.

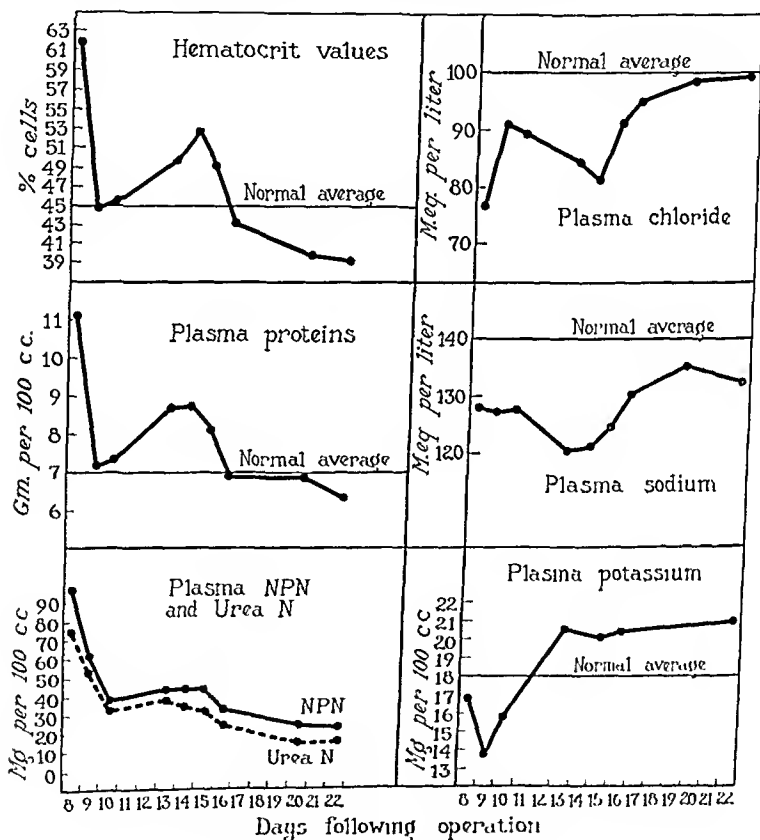


Fig. 2.—Determinations of blood chemistry.

The figures we have just presented for plasma electrolytes are not entirely typical of the crisis of adrenal cortical insufficiency, in which a high content of plasma potassium and a low content of plasma chloride and sodium usually are to be found, but with sodium depleted to a greater extent than chloride. Furthermore, the extremely small quantities of sodium and chloride in the urine on days on which extra salt was not administered does not suggest adrenal cortical insufficiency.

The physiologic basis for cholorrhea is entirely unknown. The present case and the others in the literature amply document the statement that cholorrhea apparently is a manifestation of serious hepatic damage. Presumably, the damaged liver loses the capacity to excrete bilirubin and to form bile salts while it retains the ability to excrete chloride and base in concentrations which are higher than those present in the blood. Brand has stated that bile shows a remarkable tendency to maintain a constant osmotic pressure which is equal to that of the plasma and that variations in one of the constituents of bile are compensated for by sufficient alteration of others to maintain the normal osmotic pressure. On this basis one of the fundamental disturbances in cholorrhea is a decreased ability of the hepatic parenchyma to excrete bile acids. Under such circumstances the chloride content of the bile is necessarily greater than that of normal hepatic bile.<sup>10</sup>

#### SUMMARY

The syndrome of postoperative cholorrhea occurs occasionally as a complication of surgery of the biliary tract. It is perhaps most frequently encountered among patients who have hepatic disease associated with stones in the common bile duct, but also may be encountered in the presence of chronic biliary obstruction from other causes. It is characterized by profuse drainage of pale, thin bile containing markedly decreased quantities of bilirubin and bile salts and excessive concentrations of chloride and mineral base. The cases heretofore reported lead the investigator to believe that the presence of this condition is a serious prognostic sign. Loss of fluids and of large quantities of electrolytes by means of such excessive biliary drainage may lead to dehydration, hypochloremia, and circulatory collapse. It seems probable that deaths may have occurred from these secondary factors rather than from hepatic deficiency.

A case is presented in which cholecystitis and stones in the common bile duct associated with cirrhosis of the liver and evidence of impaired hepatic function produced certain clinical and chemical features bearing a superficial resemblance to Addison's disease. Postoperative cholorrhea, its implications at first unrecognized, led to profound electrolyte depletion, hypochloremia, hemoconcentration, and circulatory collapse. Adequate and persistent replacement of salt and mechanical termination of the external flow of bile were followed by completely satisfactory convalescence.

#### REFERENCES

1. Brand, J.: Beitrag zur Kenntniss der menschlichen Galle, *Pflüger's Arch. f. d. ges. Physiol.* 90: 491-522, 1902.
2. Collier, F. A., and Maddock, W. G.: Water Balance in Surgical Conditions, *Internat. Clin. (s. 11)* 3: 191-215, 1934.
3. Collier, F. A., Dick, V. S., and Maddock, W. G.: Maintenance of Normal Water Exchange With Intravenous Fluids, *J. A. M. A.* 107: 1522-1527, 1936.

first week is shown to have exceeded the intake, although not by impressive amounts (Fig. 1). Except for the solution of sodium chloride administered intravenously the first few days postoperatively, the intake contained very little salt, for the patient ate little and the fluids taken by mouth, although they were of fairly satisfactory volume, were virtually salt-free. By contrast, the fluid excreted, especially the bile, contained large amounts of salt. On this basis the resultant hypochloremia and circulatory collapse may be explained.

An estimate of the probable daily salt balance has been made for the entire postoperative period. These balances are shown graphically in Fig. 3. From the diet record was calculated the maximal possible intake of chloride, and for days on which no laboratory data were available, a minimal output of chloride in the urine was postulated. The average

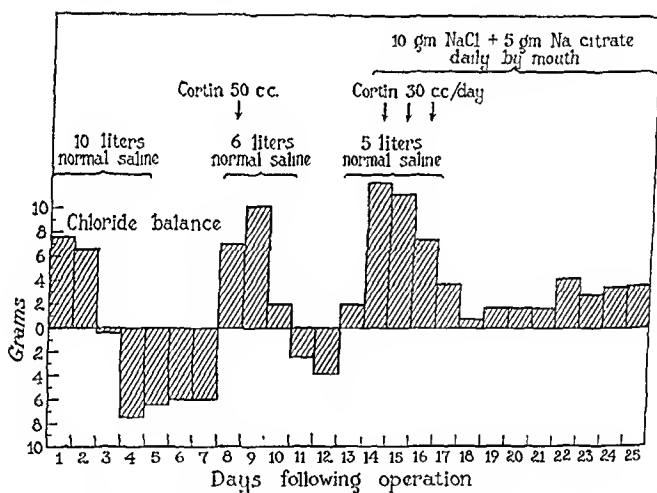


Fig. 3.—Estimated chloride balance. The difference between the estimated intake and estimated output of chloride ion is shown as "grams retained" or "grams lost" per day. Marked chloride depletion preceded the appearance of shock on the eighth postoperative day.

values for chloride were applied to all bile excreted. The differences between the values for intake and output of chloride were assumed to represent a conservative measure of the loss of salt when such loss occurred. It may be seen from the graph that the time of circulatory collapse is preceded by several days, during which the excretion of chloride exceeded the intake by large amounts, and that a similar negative balance was inadvertently allowed to occur during several days preceding the second period of hemoconcentration. By the time the latter had occurred, the underlying disturbance was recognized; extra salt and extra sodium were administered regularly thereafter, partial closure of the T-tube was expedited and subsequent recovery was without further incident. There is no reason to believe that the adrenal cortical extract administered as emergency treatment in this case played any significant role in the patient's recovery.

## HEMANGIOMA OF THE LIVER

### DISCUSSION OF SYMPTOMATOLOGY AND REPORT OF PATIENT TREATED BY OPERATION

HARRIS B. SHUMACKER, JR., M.D., BALTIMORE, MD.

(From the Department of Surgery, the Johns Hopkins Hospital)

ALTHOUGH small hemangiomas of the liver are not uncommonly seen incidentally at post-mortem examination,\* such tumors rarely grow sufficiently large to cause symptoms or signs which lead to operative treatment. Because of this fact, and possibly also because some surgeons when confronted with the problem of dealing with a blood vessel tumor in a notoriously vascular organ may have refrained from resection for fear of uncontrollable hemorrhage, the number of reported cases in which resection has been carried out is not large, and no author has published a report of more than a single case.

When I recently came upon a large hepatic hemangioma during a laparotomy, the puzzling question presented itself whether the tumor was causing the symptoms of which the patient complained and whether resection would relieve her of her distress. Like certain other lesions which are ordinarily small and asymptomatic and rarely are large enough to produce complaints, the symptoms which may be attributed to hemangioma of the liver are not commonly known, the criteria upon which a pre-operative diagnosis may be postulated are not fully understood, and the efficacy of treatment is not definitely appreciated. I have consequently felt it advisable to report this case and to analyze the case records in the literature in regard to the clinical picture which these tumors present and the outcome of operative treatment. I shall deal only briefly with the technique of resection. From time to time certain fundamental contributions to the operative removal of liver tumors in general and of hemangiomas in particular have been made, and the problem has been discussed in several recent papers.<sup>73, 75</sup> I shall not include in this study malignant hemangioendotheliomas.<sup>5, 77</sup>

#### CASE REPORT

C. L., a colored married female, 40 years of age, was admitted to the Johns Hopkins Hospital on April 21, 1940, complaining of epigastric discomfort. She stated that her present illness had begun at least fifteen years before and had continued except for occasional remissions which did not last more than a few weeks, and that during this time she had had nearly constant gnawing discomfort in the upper abdomen. The trouble had become steadily worse and had been especially bad in recent months. She complained of a continual feeling of fullness and of a constant "sour feeling" with occasional eructation but with little or no vomiting.

Received for publication, April 24, 1941.

\*Hemangiomas occur more often in the liver than in any other internal organ.<sup>74</sup> In the majority of instances these are solitary tumors.

4. Cutler, H. H., Power, M. H., and Wilder, R. M.: Concentrations of Sodium, Chloride and Potassium in the Blood Plasma and Urine of Patients With Addison's Disease: Their Diagnostic Significance, *Proc. Staff Meet., Mayo Clin.* 13: 244-249, 1938.
5. Foster, M. G., Hooper, C. W., and Whipple, G. H.: The Metabolism of Bile Acids. II. Normal Fluctuations in Healthy Bile Fistula Dogs, *J. Biol. Chem.* 38: 367-377, 1919.
6. Foster, M. G., Hooper, C. W., and Whipple, G. H.: The Metabolism of Bile Acids. III. Administration by Stomach of Bile, Bile Acids, Taurine and Cholic Acid to Show the Influence Upon Bile Acid Elimination, *J. Biol. Chem.* 38: 379-392, 1919.
7. Greene, C. H., Walters, Waltman, and Fredericksen, C. H.: The Composition of the Bile Following the Relief of Biliary Obstruction, *J. Clin. Investigation* 9: 295-310, 1930.
8. Kagan, B. M.: A Simple Method for the Estimation of Total Protein Content of Plasma and Serum. I. A Falling Drop Method for the Determination of Specific Gravity, *J. Clin. Investigation* 17: 369-372, 1938.
9. Mehlhor, Edward: Die Cholorrhoe, eine ungewöhnliche Komplikation nach Gallen-operationen, *Zentralbl. f. Chir.* 59: 2940-2942, 1932.
10. Reinhold, J. G., and Wilson, D. W.: The Acid-Base Composition of Hepatic Bile, *Am. J. Physiol.* 107: 378-387, 1934.
11. Sadlier, J. E.: Excessive Drainage Complicating Surgery Upon the Common Bile Duct, *Am. J. Obst.* 75: 135-144, 1917.
12. Scudder, John: Shock; Blood Studies as a Guide to Therapy, Philadelphia, 1940, J. B. Lippincott Co., 315 pp.
13. Snell, A. M.: Clinical Types of Hepatic Insufficiency and Their Treatment, *J. Iowa M. Soc.* 31: 1-7, 1941.
14. Sobotka, Harry: *Physiological Chemistry of the Bile*, Baltimore, 1937, Williams and Wilkins, Co., 202 pp.
15. Tschopp, E.: Quoted by Sobotka.<sup>14</sup>
16. Walters, Waltman, and Parham, Duncan: Renal and Hepatic Insufficiency in Obstructive Jaundice, *Surg., Gynec. & Obst.* 35: 605-609, 1922.
17. Wangenstein, O. H.: Complete External Biliary Fistula; a Potential Serious Postoperative Complication, *J. A. M. A.* 93: 1199-1204, 1929.
18. Willson, D. M., Power, M. H., and Kepler, E. J.: Alkalosis and Low Plasma Potassium in a Case of Cushing's Syndrome: a Metabolic Study, *J. Clin. Investigation* 19: 701-707, 1940.

ulcer being suspected from time to time. When this diagnosis was thought to have been established, she was admitted to the hospital for operation.

The patient had had many other complaints. Since 1926 she had been under treatment or observation for syphilis. She had been treated off and on in the nose and throat clinic since 1927 for bilateral maxillary sinusitis, and since 1933 she had been under treatment in the protein clinic for asthma. She had been thought by some to have infectious arthritis, but in 1940 the physicians in the arthritic clinic had failed to find any evidence of arthritis and thought her joint complaints were entirely subjective. She had been seen in the gynecologic clinic on numerous occasions and had been treated for chronic salpingitis, trichomonas infection, and ureteral stricture. It seemed to be generally felt that in addition to many organic complaints she had a definite tendency to hypochondriasis. Her family history was noncontributory.

On admission the temperature was 99.4° F.; the pulse, 96; the respirations, 22; and the blood pressure, 146/90. On general examination nothing abnormal was found except a small ill-defined mass just below the xiphoid which descended with respiration and was slightly tender to palpation. It could not be outlined sufficiently well to permit an accurate opinion as to its size, contour, or consistency. The Wassermann reaction was negative, the urine essentially normal, the hemoglobin 54 per cent. The day after admission the patient was given a transfusion of 500 c.c. of citrated blood, which raised the hemoglobin to 63 per cent.

It was thought that the patient had a chronic duodenal ulcer. The presence of the mass raised the question whether she might have a gastric carcinoma with metastases to the liver.

*Operation.*—Exploratory laparotomy, excision of hemangioma of liver, April 23, 1940. Under ether anesthesia a high left paramedian incision was made, the peritoneum was opened, and the viscera were inspected. In the first portion of the duodenum was a small diverticulum, smaller than the distal phalanx of one's little finger. No ulcer was seen and the pylorus was patent and not scarred. Some observers thought there was evidence of very slight scarring on the anterior surface of the duodenum just beyond the pylorus, but this was not definite and there was no conclusive evidence that the patient had ever had a peptic ulcer. The stomach was entirely normal, as were the gall bladder and the intestinal tract. Attention was immediately attracted to a large cavernous hemangioma about the size of a man's fist, which occupied most of the left lobe and which pressed upon the upper portion of the lesser curvature of the stomach (Fig. 2). It was felt that this lesion most likely accounted for the patient's symptoms. The ligamentous attachment of the left lobe of the liver to the diaphragm was divided, permitting adequate mobilization of the lobe. Large Kelly clamps were placed across the liver about 1.5 cm. beyond the margins of the tumor, and the tumor was quickly excised by sharp dissection. The clamps held along the margin of the liver where the liver was thin, but cut through deeper in where the liver was thick. The pedicle of the lobe was being compressed between two fingers, however, and there was surprisingly little bleeding. Through and through mattress sutures of medium silk were placed just within the clamps and the clamps were removed. Release of pressure on the biliary structures demonstrated a number of bleeding points; these were clamped with hemostats and coagulated with the electrocautery. The mattress sutures had approximated the serosal edges of the liver in its thin peripheral portion, but it was impossible to accomplish this centrally because of the thickness of the liver. The bed was now dry. A cigarette drain was so placed that the end of the gauze was in contact with the denuded liver surface. The wound was closed in layers with interrupted silk sutures. The patient stood the procedure well.

Pathologic study showed the excised tumor to be a typical cavernous hemangioma, made up essentially of large sinuses filled with blood and lined by typical endothelial cells. The interstices were made up of moderately dense connective tissue.

Sometimes there was a "quivering" sensation in the upper abdomen and sometimes, she said, the gnawing discomfort was somewhat as if she could feel her heart beating in the epigastric region. She said that soda, milk, and food brought some temporary relief, but rarely for longer than an hour or an hour and a half at most. The discomfort was especially annoying at night, often waking her from a sound sleep. She had never had hematemesis or melena. She said that her weight had fluctuated greatly during the past twenty years and that she had recently lost weight.

Examination of her voluminous dispensary record showed that she had been a frequent visitor to the gastrointestinal clinic since 1927, when she first came because of upper abdominal discomfort and constipation of seven years' duration. The complaints were repeatedly the same: "gas," "misery," "gnawing" or "quivering" sensation in the "pit of the stomach." During the fourteen years of observation she had been treated with various alkalis, diet, mineral oil, belladonna, bromide, and hyoseyamus compound. There were fluctuations in her distress but rarely relief for any length of time. She had had numerous gastric analyses. The fasting free acid varied from 14 to 42, the total from 39 to 78. In 1931, after the administration of histamine, the free acid was 66, the total 76. From time to time gastrointestinal fluoroscopy was done. In 1927 the stomach was said to be atonic but



Fig. 1.—Gastrointestinal x-rays. A. Before operation, April, 1940. The pressure defect on the lesser curvature from an extrinsic mass and the deformity of the duodenal bulb were constant in all films. B. After operation, May, 1940. The pressure from the extrinsic mass is no longer present. Deformity of the duodenal bulb persists.

without intrinsic lesion. In 1937 the stomach and duodenum were described as normal. In March, 1939, the pylorus was said to be spastic. X-rays taken in October, 1939, showed a pressure defect of the lesser curvature from an extrinsic mass and deformity of the duodenal bulb thought to be due to an old ulcer. Two subsequent gastrointestinal series presented essentially the same picture (Fig. 1 A). Cholecystograms in 1939 showed no pathologic changes. A number of stool examinations were negative for occult blood. During the period of observation her hemoglobin varied between 60 and 70 per cent. A complete blood examination in April, 1940, was as follows: erythrocytes, 4.47 millions; hemoglobin 8.5 Gm. (60 per cent); hematocrit, 32; mean corpuscular volume, 72 c. micron<sup>3</sup>; mean corpuscular hemoglobin, 19 micronograms; mean corpuscular hemoglobin concentration, 27 per cent; sedimentation rate, 7 (corr.); ieterns index, 4. The impression had varied,

When the patient first left the hospital, she complained of a sense of fullness and occasionally of slight regurgitation upon eating a large meal, but this difficulty soon ceased on a regimen of six small daily feedings which she followed for a few weeks. After this she was able to take a normal diet without difficulty. Gastrointestinal x-rays one month after operation showed normal stomach motility and the same deformity of the duodenal bulb which had been noted before operation (Fig. 1 B).



Fig. 3 —Photomicrograph of peripheral portion of the tumor showing large endothelial-lined sinuses and the adjoining liver tissue.

One year after operation she looked well. She had gained in weight and examination was essentially negative except for a keloidal change in the abdominal scar. The liver was not palpable. There was no abdominal tenderness. She stated that she was definitely better than before the operation but was not entirely relieved of her trouble. For ten months she had had good appetite and digestion; bowels had moved regularly with the use of mineral oil; the sense of fullness, the frequent eructation, and the annoying pains which she had had before operation were almost entirely absent. Ordinarily she was not aware of her "stomach"; she complained much more of pains in her joints and in her eyes; and she volunteered that she felt quite well as long as she could keep her mind diverted and did not think too much about herself. During the past two months, however, there had been a return in a mild form of some of her old complaints. She had frequently had a "sick feeling" in her epigastrium which she found difficult to describe and at times a great deal of eructation. These symptoms could be relieved with food, milk, or even water. The growing pains had not returned, nor had the "quivering sensa-



The normal liver surrounding the tumor showed no scarring but some mononuclear inflammatory infiltration in the portal spaces (Fig. 3).

The postoperative course was uneventful. The patient was comfortable. For five days there was a slight elevation of temperature which only once exceeded 100° F. For a few days there was light serohemorrhagic drainage but no biliary drainage. The drain was gradually shortened and was removed on the seventh day. She was discharged on the sixteenth postoperative day, the wound being entirely healed. A bromsulfalein liver function test the preceding day showed less than 5 per cent retention.

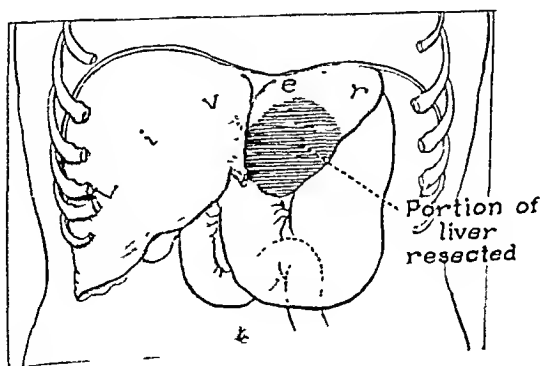
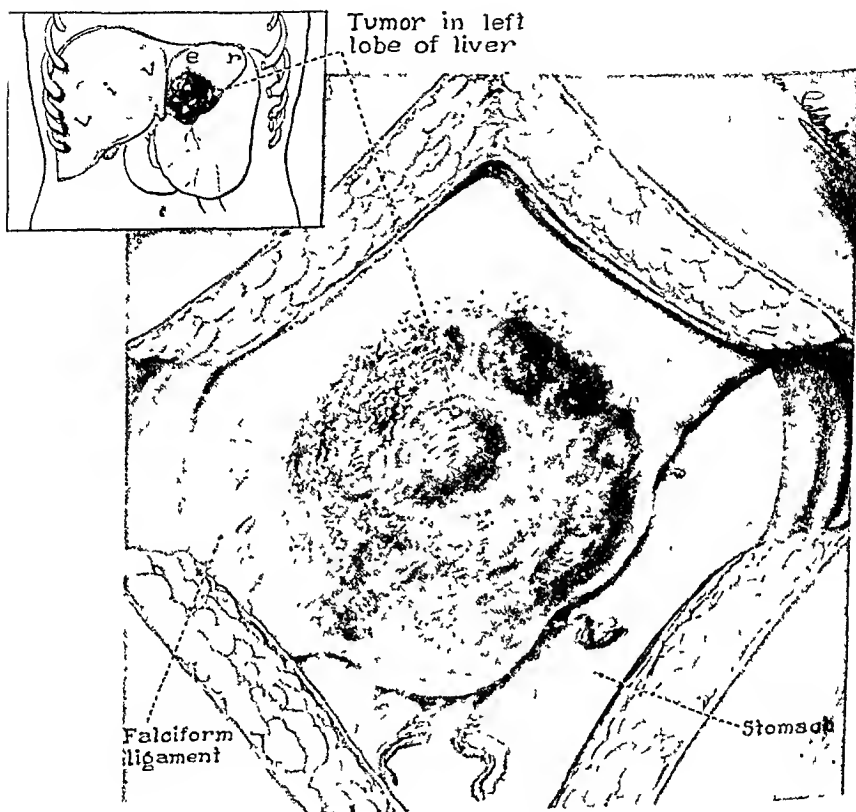


Fig. 2.—Drawing of the tumor made at operation

initiated the illness in nearly one-half of all the patients. This was the case in 27 patients. In 3, in all of whom there had been spontaneous rupture of the hemangioma, the illness was of short duration and suggested acute appendicitis, ruptured tubal pregnancy, or peritonitis.<sup>15, 43, 72</sup> In most, however, the complaints were of a chronic nature, beginning in some instances as long ago as ten or twenty years before operation. The average duration of symptoms was nearly five years. In 17 patients the complaints were largely referable to the stomach. Some are said to have had "stomach trouble" or "indigestion"; in most there was definite epigastric distress or pain, frequently postprandial. An occasional patient localized his discomfort in the right or left upper quadrant, but more commonly it was in the midepigastrium. Sometimes the discomfort was described as of an unusual nature such as "whirling," "tearing," or "dragging." Nausea, vomiting, and anorexia were not uncommon. One patient had definite melena and hematemesis.<sup>45</sup> A few had difficulty in swallowing. In general, the symptoms at the beginning of the illness were commonly such as to direct attention to the stomach, although subsequently the belief was often held that there was some extragastric lesion because all of these patients had a palpable tumor at the time of operation. In 7 patients, on the other hand, the symptoms rather suggested gall bladder or biliary tract disease; in 3 of these the symptoms were apparently due to the hemangioma as resection of the tumor brought about relief of symptoms. Interestingly enough, in a fourth<sup>70</sup> the hemangioma caused a hydrops of the gall bladder by pressure on the neck of the gall bladder, and excision without further operative procedures effected a cure. In 3 instances there was associated gall bladder disease and hemangioma of the liver. In 1 patient<sup>71</sup> the gall bladder appeared normal and the hemangioma alone was resected; the complaints, however, continued until a cholecystectomy was subsequently done. The pathologic report was chronic cholecystitis. In another<sup>25</sup> the hemangioma was resected at the same time the cholecystectomy was done. In the third<sup>70</sup> the hemangioma was discovered only at autopsy, having been overlooked in three successive operations for cholelithiasis.

One patient complained of headache, vertigo, anorexia, and fatigability; another,<sup>1</sup> a patient who had suffered a spontaneous rupture of a hemangioma, complained only of weakness; in a few cases the history is not given.

In only a few cases is it definitely stated that a tumor was not palpable, and in 54 a tumor was easily felt. In general, nothing characteristic was noted about the tumor mass. In 1 instance a murmur on auscultation and a history of a whirling or buzzing sensation led to the correct diagnosis before operation.<sup>4</sup> Another tumor was so compressible as to lead the examiner to suggest the correct diagnosis.<sup>20</sup> Ordinarily, however, nothing unusual was noted on palpation of the mass. Unfortunately, in almost all the cases, as in my own, auscultation

tions" which she said constituted the most distressing complaint before operation. It is apparent that she has by no means obtained complete relief and it remains to be seen whether her symptoms will diminish or increase with the passage of time.\*

### DISCUSSION

I have found in the literature 66 cases of benign hemangioma of the liver in which operation has been performed.† My case brings the total to 67. In 56 of these the tumor was resected.

The youngest patient in this series was 6 years old,<sup>54</sup> the oldest 76;<sup>5</sup> and the average age was 44 years. Operation was most commonly performed in the third and fourth decades (58 per cent). Seventy-five per cent were between 30 and 60 years old at the time of operation.

Females were affected in a ratio of about 4.5 to 1 male. Fifty-one of 62 patients on whom data are available were females.

In about one-half of the cases the initial complaint was of a tumor mass in the epigastrium or some equivalent symptom such as increase in the size of the abdomen, and about one-half of the patients first complained of pain or some digestive disturbance. Twenty-eight of 61 patients on whom data are available had first some such complaint as a tumor or abdominal swelling, and at least 21 of them were aware of a definite tumor mass. In addition, 4 patients had their attention called to the presence of a tumor by their physician; 2 of these never developed any symptoms. In 12 other instances in which the illness began with pain or some other symptom the patient subsequently complained of a tumor or of abdominal swelling.

The 32 patients whose initial difficulty was a tumor or abdominal enlargement had noticed this for a period of time varying from a few months to over 30 years, and on an average this complaint dated back about 5½ years. Apparently in 6 of these patients no other symptoms appeared. One complained of nothing except weakness and evening fever, 2 of slight local discomfort, 7 of a sense of weight or pressure. One had dysmenorrhea, 1 dysuria, 2 pain in the back or legs. Twelve of them complained of severe or mild epigastric pain or of a sense of heaviness, pressure, or fullness in the upper abdomen, often associated with other symptoms such as eructation, nausea, or vomiting. In some instances the distress was largely postprandial.

Not only was pain or digestive difficulty the commonest of the symptoms which subsequently appeared in the group of patients whose illness first became manifest by an abdominal tumor or enlargement, but "dyspepsia," "stomach trouble," abdominal pain or discomfort usually epigastric, nausea, vomiting, anorexia, and other gastrointestinal complaints

\*At the time of publication the patient is considerably better. She has had very little difficulty in recent months, has not required soda or other medicine, and has continued to gain weight. She says that her health has been decidedly better during the year and a half since operation than any time during the past fifteen or twenty years.

†A few papers which may contain a few additional cases are not available to me. In discussing Tinker's paper<sup>22</sup> E. Beer mentions a case of hemangioma of the liver in which he had difficulty in controlling the bleeding. No other details are given and the outcome is not stated.

initiated the illness in nearly one-half of all the patients. This was the case in 27 patients. In 3, in all of whom there had been spontaneous rupture of the hemangioma, the illness was of short duration and suggested acute appendicitis, ruptured tubal pregnancy, or peritonitis.<sup>15, 43, 72</sup> In most, however, the complaints were of a chronic nature, beginning in some instances as long ago as ten or twenty years before operation. The average duration of symptoms was nearly five years. In 17 patients the complaints were largely referable to the stomach. Some are said to have had "stomach trouble" or "indigestion"; in most there was definite epigastric distress or pain, frequently postprandial. An occasional patient localized his discomfort in the right or left upper quadrant, but more commonly it was in the midepigastrium. Sometimes the discomfort was described as of an unusual nature such as "whirring," "tearing," or "dragging." Nausea, vomiting, and anorexia were not uncommon. One patient had definite melena and hematemesis.<sup>46</sup> A few had difficulty in swallowing. In general, the symptoms at the beginning of the illness were commonly such as to direct attention to the stomach, although subsequently the belief was often held that there was some extragastric lesion because all of these patients had a palpable tumor at the time of operation. In 7 patients, on the other hand, the symptoms rather suggested gall bladder or biliary tract disease; in 3 of these the symptoms were apparently due to the hemangioma as resection of the tumor brought about relief of symptoms. Interestingly enough, in a fourth<sup>70</sup> the hemangioma caused a hydrops of the gall bladder by pressure on the neck of the gall bladder, and excision without further operative procedures effected a cure. In 3 instances there was associated gall bladder disease and hemangioma of the liver. In 1 patient<sup>71</sup> the gall bladder appeared normal and the hemangioma alone was resected; the complaints, however, continued until a cholecystectomy was subsequently done. The pathologic report was chronic cholecystitis. In another<sup>25</sup> the hemangioma was resected at the same time the cholecystectomy was done. In the third<sup>70</sup> the hemangioma was discovered only at autopsy, having been overlooked in three successive operations for cholelithiasis.

One patient complained of headache, vertigo, anorexia, and fatigability; another,<sup>7</sup> a patient who had suffered a spontaneous rupture of a hemangioma, complained only of weakness; in a few cases the history is not given.

In only a few cases is it definitely stated that a tumor was not palpable, and in 54 a tumor was easily felt. In general, nothing characteristic was noted about the tumor mass. In 1 instance a murmur on auscultation and a history of a whirring or buzzing sensation led to the correct diagnosis before operation.<sup>4</sup> Another tumor was so compressible as to lead the examiner to suggest the correct diagnosis.<sup>20</sup> Ordinarily, however, nothing unusual was noted on palpation of the mass. Unfortunately, in almost all the cases, as in my own, auscultation

tion was not carried out. The tumor was most commonly palpated in the left upper quadrant of the abdomen or just below the xiphoid. It was found to arise from the left lobe in 30 cases, from the right in 18, from the spigelian in 1, in an accessory lobe in 1, in a "*Schnurrlappen*" in 1. In 5 instances the origin was apparently from multiple lobes; 1 tumor arose from both right and left lobes, 2 from the left and quadrate lobes, 1 from the left, quadrate, and spigelian lobes, and 1 from the right and quadrate lobes. The size of the tumor was variously described; it was said to be the size of a prune, hazelnut, walnut, goose egg, gall bladder, apple, orange, man's fist, fetal head, child's head, man's head, pregnant uterus. In 17 instances where actual weights are given the tumor, generally in the collapsed state, weighed from 58 to 2,500 Gm. and averaged about 900 Gm. In 18 instances in which measurements are given the size varied from 9 by 5 cm. to 32 by 22 by 9 cm. and averaged about 12 by 12 cm. In 23 cases the tumor was more or less pedunculated; in 8 of these the pedicle was large and broad.

In 12 cases gastrointestinal x-rays were taken. In 1 case,<sup>76</sup> in which the patient had had gradually increasing difficulty in swallowing foods until finally no solids could be taken, x-rays showed considerable retention of barium in the lower portion of the esophagus, and the patient was operated upon with a preoperative diagnosis of carcinoma of the cardia. In 8 cases the stomach was seen to be pushed over to the left or downward or to have an extrinsic mass pressing upon the lesser curvature, often lengthening the lesser curvature.<sup>2, 18, 23, 58, 65, 67, 68</sup> In 1 case<sup>48</sup> the colon was displaced by a mass in the right upper quadrant. In 2 cases gastrointestinal series were said to have showed nothing abnormal.<sup>27, 69</sup> In 8 of the 11 cases in the literature the x-rays were rather similar to those in my case.

The correct diagnosis was made only twice before operation.<sup>4, 20</sup> In 4 other instances it was suggested as a possibility along with others. In a few cases the preoperative diagnosis is not given; in others numerous possibilities are listed. Tumor of the liver was suggested 13 times, hepatic echinococcus cyst twice, "liver disease" twice, tumor or cyst of the pancreas 9 times, mesenteric tumor or cyst 5 times, omental tumor 4 times, and adrenal tumor once. Renal tumor was considered twice, mobile kidney 4 times, tumor of the gall bladder 3 times, hydrops 3 times, cholecystitis twice, cholelithiasis once. Ovarian tumor or cyst was considered in 7 cases, uterine myoma in 1. Carcinoma of the stomach was suspected in 2 cases, peptic ulcer in 1. Other diagnoses were acute appendicitis, abdominal abscess, peritonitis, intestinal tumor.

In 56 instances resection was carried out. Only 1 of these patients died. This patient had a tumor in the right lobe lateral to the gall bladder in the periphery of the liver without pedicle. During the operation there was shock although comparatively little blood was lost, and the patient died in eighteen hours.<sup>41</sup> In all other instances resection was attended by recovery. Various procedures were employed. In 23 cases

the tumor was pedunculated, in 8 of which the pedicle was very large. The problem in these cases, even when the pedicle was very broad and thick, was greatly simplified. When small, the pedicle was simply ligated with a transfixing ligature and divided. With the larger pedicles several hemostatic sutures were necessary. Sometimes a V-incision was made through the pedicle to permit approximation of the serosal surfaces. In one of the early cases Rosenthal,<sup>62</sup> finding a sort of pedicle, placed an elastic tourniquet about it, extra-abdominalized the mass with a needle through the pedicle, cut through the pedicle with the cautery, and packed with iodoform gauze. In another early case, Keen,<sup>32</sup> confronted with a large tumor in the left lobe, cut into the liver on both sides, thus making an artificial pedicle. Elastic rubber tubes were secured about its base as a tourniquet, iodoform gauze was packed below the tourniquet, and the tumor, tourniquet, and gauze were brought out through the wound. The tourniquet was removed some days later, the tumor excised, and the defect closed with skin grafts. In another early case Pfannenstiel<sup>28</sup> also made an artificial pedicle in a similar manner. He excised the tumor and sutured the cut surface of the liver to the abdominal wall, thus extraperitonealizing it. Beck<sup>3</sup> used rubber catheters over iodoform gauze as a tourniquet, extra-abdominalized the mass with hat pins through the pedicle, and removed the tumor. Israel<sup>29</sup> also used a rubber tube tourniquet and silk ligature, bringing the tourniquet out through the wound. In the first reported case of resection Eiselsberg<sup>19</sup> utilized the cautery and pack. Another early case in which the cautery and pack were used is that of Beck.<sup>4</sup> Smoley<sup>55</sup> used elastic bands as a tourniquet, mass ligatures, and the cautery. He then sutured the liver and employed no drainage. In the more recent cases such devices have not ordinarily been necessary. The cautery has a definite place in controlling bleeding. In Eiselsberg's original case<sup>19</sup> the operator first cut very close to the tumor mass and there was considerable bleeding. When incision was made further out in the normal liver substance, there was much less bleeding. This principle of never cutting through the tumor itself but through normal liver tissue was re-emphasized by Horsley.<sup>27</sup> Eckles<sup>14</sup> found the use of rubber-shod clamps across the liver substance of considerable help. Similarly, placing Kelly clamps across the liver, as was done in my case, may be helpful. V-incisions into the liver substance or into a large pedicle often permit approximation of the serosal surfaces where this would otherwise be impossible. Hemostatic mattress sutures along the cut margin of the liver are useful in controlling bleeding. Adequate mobilization of the liver through division of the ligamentous attachment to the diaphragm is an important aid. Temporary compression of the hilar structures, as I did in my case, is very helpful in controlling bleeding. This maneuver is also useful because grasping the hilum between one's fingers permits one to deliver the lobe better into the operative field and to restrict its motion during the resection. Altogether the problem of re-

tion was not carried out. The tumor was most commonly palpated in the left upper quadrant of the abdomen or just below the xiphoid. It was found to arise from the left lobe in 30 cases, from the right in 18, from the spigelian in 1, in an accessory lobe in 1, in a "*Schnurrlappen*" in 1. In 5 instances the origin was apparently from multiple lobes; 1 tumor arose from both right and left lobes, 2 from the left and quadrate lobes, 1 from the left, quadrate, and spigelian lobes, and 1 from the right and quadrate lobes. The size of the tumor was variously described; it was said to be the size of a prune, hazelnut, walnut, goose egg, gall bladder, apple, orange, man's fist, fetal head, child's head, man's head, pregnant uterus. In 17 instances where actual weights are given the tumor, generally in the collapsed state, weighed from 58 to 2,500 Gm. and averaged about 900 Gm. In 18 instances in which measurements are given the size varied from 9 by 5 cm. to 32 by 22 by 9 cm. and averaged about 12 by 12 cm. In 23 cases the tumor was more or less pedunculated; in 8 of these the pedicle was large and broad.

In 12 cases gastrointestinal x-rays were taken. In 1 case,<sup>76</sup> in which the patient had had gradually increasing difficulty in swallowing foods until finally no solids could be taken, x-rays showed considerable retention of barium in the lower portion of the esophagus, and the patient was operated upon with a preoperative diagnosis of carcinoma of the cardia. In 8 cases the stomach was seen to be pushed over to the left or downward or to have an extrinsic mass pressing upon the lesser curvature, often lengthening the lesser curvature.<sup>2, 18, 23, 58, 65, 67, 68</sup> In 1 case<sup>48</sup> the colon was displaced by a mass in the right upper quadrant. In 2 cases gastrointestinal series were said to have showed nothing abnormal.<sup>27, 69</sup> In 8 of the 11 cases in the literature the x-rays were rather similar to those in my case.

The correct diagnosis was made only twice before operation.<sup>4, 29</sup> In 4 other instances it was suggested as a possibility along with others. In a few cases the preoperative diagnosis is not given; in others numerous possibilities are listed. Tumor of the liver was suggested 13 times, hepatic echinococcus cyst twice, "liver disease" twice, tumor or cyst of the pancreas 9 times, mesenteric tumor or cyst 5 times, omental tumor 4 times, and adrenal tumor once. Renal tumor was considered twice, mobile kidney 4 times, tumor of the gall bladder 3 times, hydrops 3 times, cholecystitis twice, cholelithiasis once. Ovarian tumor or cyst was considered in 7 cases, uterine myoma in 1. Carcinoma of the stomach was suspected in 2 cases, peptic ulcer in 1. Other diagnoses were acute appendicitis, abdominal abscess, peritonitis, intestinal tumor.

In 56 instances resection was carried out. Only 1 of these patients died. This patient had a tumor in the right lobe lateral to the gall bladder in the periphery of the liver without pedicle. During the operation there was shock although comparatively little blood was lost, and the patient died in eighteen hours.<sup>41</sup> In all other instances resection was attended by recovery. Various procedures were employed. In 23 cases

moved at operation. An important factor in all of these deaths was the spontaneous rupture of the tumor before, during, or after operation, or bleeding from tapping or incising the tumor at operation.

Two patients have been treated with considerable success with x-ray therapy; 1 had an inoperable tumor of the right lobe,<sup>58</sup> the other a tumor in the right lobe several months after a hemangioma of the left lobe had been resected.<sup>45</sup>

In general, those patients who have undergone resection have done well. The postoperative course has ordinarily been smooth and not unduly long. Prolonged drainage has been unusual, and except in a few cases there has been no significant biliary drainage. The ultimate results have been good, most reports stating that the patient remained well. A number of patients were entirely well when seen one and one-half to two years after operation,<sup>11, 16, 62, 67, 72</sup> and Beek's patient was well ten years after operation.<sup>4</sup> Siebner's patient<sup>67</sup> had to have a repair of postoperative hernia two years after resection, but had been relieved of the symptoms of which she had complained. Perthes' patient,<sup>74</sup> a 6-year-old girl who underwent resection of the entire left lobe, died ten months later with ascites and dyspnea. Autopsy permission was not obtained. In several other instances the entire lobe has been removed and the patients have remained well.<sup>20, 72, 75</sup> The patient reported by Nossen<sup>71</sup> was well after operation but died in two years of carcinoma of the rectum. At autopsy there were seen several angiomata of the liver, and the author concluded that they must have been multiple at the time of operation. As I have stated before, the patient reported by Razemon and Decoulx<sup>70</sup> was not relieved after excision of the hemangioma until she returned some months later and underwent a cholecystectomy. Two months after Morris<sup>4</sup> resected a hemangioma of the left lobe the patient returned with a mass in the right lobe which was treated successfully with x-ray. My patient has not obtained complete relief. Such difficulties were few, however, and most of the patients reported in the literature were apparently entirely relieved of their complaints by resection of the tumor.

#### SUMMARY

Hemangiomas occur more commonly in the liver than in any other internal organ. They are usually small and asymptomatic, but occasionally they grow to sufficient size to cause symptoms. The disease affects females more often than males. It is found in all age groups but is especially common in the third, fourth, and fifth decades. The symptoms, other than those of the tumor mass itself or abdominal swelling, are due to pressure on other organs by the mass and vary with the location of the tumor. All lobes of the liver give rise to these tumors, but the left lobe more commonly than the others. About one-half the patients with hemangioma of the liver who seek surgical aid have their attention called to the condition by the presence of a tumor mass or by enlargement of the abdomen. The commonest symptoms which subsequently develop



section is not so difficult as one might expect it to be, and if care is used the procedure is apt to be attended by little hemorrhage.

It should be emphasized that one should never cut into the tumor itself nor even aspirate it, for such maneuvers have proved fatal on several occasions. In Leech's case<sup>12</sup> the tumor was tapped; there was severe bleeding, sutures were ineffective, only tearing the tumor and causing more bleeding, and the patient died in two hours. M'Weeney<sup>16</sup> incised the tumor, which bled profusely, and although the patient rallied from the severe hemorrhage, he died a week later of hematemesis. Ljunggren<sup>40</sup> punctured the tumor, and free bleeding resulted. He was able, however, to proceed with resection and recovery ensued. Cripps<sup>13</sup> also caused severe bleeding by incision into the tumor but was able to do a resection, and his patient survived.

A very real danger associated with hemangioma of the liver is rupture of the tumor. Dahle<sup>15</sup> reports a case diagnosed erroneously as acute appendicitis in which a hemangioma of the liver had ruptured. At the time of operation there was no longer any active bleeding although there was blood in the peritoneal cavity. The tumor was packed and recovery ensued. Tinker<sup>12</sup> found an actively bleeding hemangioma of the liver in a patient who had right lower abdominal pain and tenderness. A resection was done and the patient recovered. Others, however, were not so fortunate. Karp<sup>31</sup> had a patient in whom there was a spontaneous rupture, who was thought by the family doctor to have a ruptured tubal pregnancy. Because of a palpable mass the diagnosis was changed before operation to a cystic tumor of the liver. At operation the tumor was packed, and the patient died on the tenth postoperative day. Marekstadt<sup>43</sup> had a patient in whom there was spontaneous rupture of an hepatic hemangioma, diagnosed before operation as peritonitis; the tumor was packed at operation and the patient died in two days. Pozzi's patient,<sup>57</sup> who had a spontaneous rupture of a hemangioma, died two hours after exploration. Freund's patient<sup>10, 61</sup> apparently suffered a spontaneous rupture during the exploration and died in one hour. Hammer<sup>25</sup> reports the death of a 7-day-old infant which was apparently due to a spontaneous rupture of a hemangioma of the liver, and Kissinger and his co-workers<sup>13</sup> report the same accident in a 3-day-old child. Leflaive<sup>30</sup> describes another case of a patient who had apparently bled from a hemangioma of the liver and at autopsy was found to have peritonitis. Several other similar autopsy cases are mentioned in the literature.<sup>17, 50</sup>

✓ From these experiences it is evident that spontaneous rupture of a hemangioma is a very real danger, that such tumors should never be incised or punctured at operation, and that if bleeding from a hemangioma occurs, better results may be expected from resection than from packing.

In contrast to the single death in 56 cases in which resection was done, there were 5 deaths among the 11 cases in which the tumor was not re-

16. Dahlgren, K.: Fall von kavernösem Angiom in der Leber nebst einigen Worten über Leberresektion, Nord. med. Arkiv. (Kirurgi) 2: 1-24, 1902.
17. Delbet, P.: Angiome du bord antérieur du foie. Extirpation après resection hépatique. Guérison, Paris chir. 4: 1117-1120, 1912.
18. Eckles, B. F.: Hemangioma of the Liver, Virginia Med. Monthly 54: 46-50, 1927.
19. Eiselsberg: Abtragung eines Cavernoms der Leber, Wien. klin. Wchnschr. 6: 1-3, 1893.
20. Filippini, G.: Sopra due resezioni di tutto il lobo sinistro del fegato per neoplasmi, Policlinico (sez. chir.) 8: 222-239, 1901.
21. Fleischmann, C.: Tumor cavernosus der Leber, Wiener klin. Wchnschr. 29: 632, 1916.
22. Gasparian, G. I.: Ueber die primären Lebergeschwülste, Arch. f. klin. Chir. 153: 435-474, 1928.
23. Genkin, I. I.: Operative Treatment of Cavernous Hemangiomas of the Liver, Sovet. Khir. 5: 157-160, 1935.
24. Geschichter, C. F., and Kearsberg, L. E.: Tumors of Blood Vessels, Am. J. Cancer 23: 568-591, 1935.
25. Hammer, F.: Beiträge zur Pathologie des Neugeborenen, Ztschr. f. Geb. u. Gynäk. 50: 213-232, 1903.
26. Hanks, H. T.: Angioma of the Liver, Am. J. Obst. 25: 229, 1892.
27. Horsley, J. S.: Cavernous Angioma of the Liver, Interstate M. J. 23: 347-350, 1916.
28. Iriarte, I., and Olivera, C.: Angioma de hígado, La semana med. 35: 293-294, 1928.
29. Isrnel, J.: Ein Fall von Extirpation eines Lebercavernoms, Berl. klin. Wchnschr. 48: 662, 1911.
30. Jarufe, J. M., and Company, J.: Kavernöses Angiom der Leber unter dem Bild der Choledochuskompression, Rev. cir. Barcelona 10: 126-133, 1935.
- Abst. Zentralorgnn. f. d. ges. Chir. u. ihre grenzg. 77: 609, 1936.
31. Knip, M.: Spontanruptur eines Leber Hämangioms, Zentralbl. f. Chir. 58: 1435-1436, 1931.
32. Keen, W. W.: Removal of an Angioma of the Liver by Elastic Constriction External to the Abdominal Cavity, With a Table of 59 Cases of Operation for Hepatic Tumors, Pennsylvania M. J. 1: 193-204, 1897.
33. Kissinger, C. C., Sternfeld, E., and Zuker, S. D.: Rupture of a Cavernous Hemangioma as a Cause of Death in a Newborn Infant, Ohio State M. J. 36: 383-384, 1940.
34. König: Verhandl. d. deutsche Gesellsch. f. Chir. 22nd Congress, p. 11, 1893.
35. König: Leberresektion, Deutsche med. Wchnschr. 37: 524-525, 1911.
36. Krause, W.: Operative Entfernung einer Kavernös entarteten Nebenleber, Zentralbl. f. Chir. 54: 1498-1501, 1927.
37. Kunstadter, R. H.: Hemangio-Endothelioma of the Liver in Infancy. Case Report and Review of the Literature, Am. J. Dis. Child. 46: 803-810, 1933.
38. Langer, P.: Erfolgreiche Extirpation eines grossen Hämangioms der Leber, Arch. f. klin. Chir. 64: 630-648, 1901.
39. Leflaive, L.: Angiome du foie. Autopsie. Examen microscopique, Bull. de la Soc. anat. de Paris 1: 379-383, 1887.
40. Ljunggren, C. A.: Zur Kenntnis des progredienten Leberkavernomes, Nord. Med. Archiv. 18: 19, 1902.
41. MacNaughton-Jones, H.: Large Angioma of the Liver Simulating Movable Kidney. Operation, Brit. Gynaec. J. 17: 40-43, 1901.
42. Mantle, A.: An Unusually Large Angioma of the Liver, Brit. M. J. 1: 365-366, 1903.
43. Murekstadt, K. O.: Ueber geplatzte Hämangiome der Leber, Deutsche Ztschr. f. Chir. 250: 37-43, 1934.
44. Markow, N.: Ueber das kavernöse Leberangiom. Shurnal sovremenn Chir. 11: 117; abst. Zentralbl. f. Chir. 55: 1214, 1928.
45. Morris, J. H.: Hemangioma of Liver. Successful Resection of Left Lobe, Ann. Surg. 111: 147-159, 1940.
46. McWeeney, E. J.: Enormous Angioma of Liver, J. Path. & Bact. 16: 401-403, 1912.
47. Neuhm, P.: Ein Fall von Leberkavernom, Zentralbl. f. Chir. 58: 1575-1577, 1931.
48. Nettrour, W. S.: Angioma of the Liver; Adenocarcinoma of the Suprarenal Gland; Report of Two Cases, Proc. Staff Meet. Mayo Clin. 11: 710-713, 1936.

are upper abdominal distress and gastrointestinal complaints, and such complaints initiate the illness in almost one-half the patients. These symptoms are such as to make one think first of some chronic gastric or duodenal lesion, but almost invariably by the time the patient presents himself for operative relief a tumor mass has become palpable which alters the diagnosis. In some patients the symptoms simulate biliary tract disease; in others they are more suggestive of an ovarian or uterine tumor. Spontaneous rupture of the tumor sometimes occurs, and this carries with it grave risk.

The correct diagnosis is difficult to make before operation. A mass is generally palpable and can ordinarily be identified as arising from the liver. There may be nothing characteristic about the tumor. Unusual compressibility or the presence of a bruit over the mass should make one suspect that the lesion may be a hemangioma. Sometimes a history of a peculiar buzzing or whirring sensation is of help in establishing the diagnosis. Gastrointestinal x-rays are frequently of considerable aid. Most commonly such studies demonstrate an extrinsic mass pressing upon the lesser curvature of the stomach, often lengthening it, and sometimes displacing the stomach downward and to the left.

When the tumor causes symptoms or presents a large asymptomatic mass, the treatment is resection. This procedure is ordinarily feasible and can be carried out with relative safety. One should never incise or aspirate the tumor as uncontrollable bleeding may occur. If there is bleeding from such a procedure or from spontaneous rupture, resection is preferable to packing. The postoperative course is ordinarily smooth and not prolonged, and the end results are good.

#### REFERENCES

1. D'Agata: Angio-cavernoma Hepatis, Resezione del fegato, Guarigione, *Rassegna intern. di Clin. e Terap.* Schutti in onore di E. Burei. p. 193, 1930 (cited by Jarufy and Company).
2. Alivisatos, A. S.: Angiome du foie simulant une tumeur, probablement néoplastique, de l'estomac, *Bull. et mém. Soc. méd. d. hôp. de Paris* 44: 1191-1193, 1920.
3. Beck, C.: Surgery of the Liver, *J. A. M. A.* 38: 1063-1068, 1902.
4. Beck: Cited by Thole.
5. Bendiek, E.: Zur Kenntnis der atypischen malignen Hemangio-Endotheliome der Leber, Frankfurt. *Ztschr. f. Path.* 53: 234-243, 1939.
6. Birsch-Hirschfeld: *Pathologische Anatomie*, Leipzig, F. C. W. Vogel, p. 615.
7. Brown, H. H.: Excision of a Large Angioma of the Liver in a Diabetic, *Brit. M. J.* 1: 232, 1937.
8. Burei, E.: Cited by Pelligrini.
9. Cascino, R.: Intervento in un caso raro di emangio-cavernoma epatico, *Arch. ital. di chir.* 51: 89-98, 1938.
10. Chiari: *München. med. Wehnschr.* 56: 1615, 1909.
11. Clar, F.: Cavernom der Leber, *Med. Klin.* 2: 1746-1747, 1928.
12. Colleoni, L. Z.: Resezione dell'ul sinistra del fegato per cavernoma, *Gaz. d. osp. d. clin. Milano* 34: 807-809, 1913.
13. Cripps, H.: Large Naevoid Tumor Removed From Liver, *Brit. M. J.* 2: 18, 1903.
14. Czerny: Cited by Pelligrini.
15. Dahle, M.: Angioma hepatis med raptur og blødning til bukholen, *Nord. med.* (Med. rev., Bergen) 4: 3334-3336, 1939.

## SPLENECTOMY

### A METHOD OF MOBILIZING THE SPLEEN IN THE PRESENCE OF DENSE ADHESIONS

J. D. RIVES, M.D., NEW ORLEANS, LA.

*(From the Department of Surgery, Louisiana State University School of Medicine)*

THE DIFFICULTY of removal of the spleen is directly proportional to the extent and density of the adhesions about it. Those hands near its anterior margin may be readily ligated and divided, but those posterior to its long axis cannot be properly visualized and must be torn or divided blindly. The most practical and most widely employed method of dealing with this difficulty is that popularized by W. J. Mayo. After all accessible adhesions have been ligated and divided, the remaining attachments are rapidly torn with the hand, the spleen is delivered into the wound, and the bed from which it has been lifted is quickly packed with very hot, moist gauze (Fig. 1). This is a very satisfactory method in most instances, but the adhesive bands usually contain large veins, and furious hemorrhage occurs and continues until the pack is in place and the splenic pedicle has been secured. If the adhesions are tougher than the capsule of the spleen, as is often the case, deep laceration of the organ occurs and another source of profuse bleeding is added. Until the spleen is completely delivered, neither packing of its bed nor control of its pedicle, which is the only effective method of controlling bleeding from the spleen, is practicable. Consequently, if the mobilization is not carried out rapidly, the hemorrhage may prove fatal before it can be controlled.

The adhesions may be extremely tough or there may be an almost complete fusion of the visceral and parietal peritoneum, either of which conditions may make it impossible to deliver the spleen rapidly by the usual method. Most authorities agree that under such circumstances it is best not to attempt splenectomy, and not a few surgeons, including myself, on at least one occasion have realized the wisdom of this view after it was too late.

Several procedures have been proposed for solution of the difficulty. Lanz and others have suggested ligating the splenic artery and leaving the spleen in place when removal is impracticable. Szendy ligated the entire pedicle and partially exteriorized and eviscerated the spleen, after which he packed the capsule tightly with gauze. Obviously these are more or less unsatisfactory substitutes for splenectomy.

Four years ago when confronted with the problem of removal of a spleen, the convex surface of which was completely fused with the parietal peritoneum, I devised, under the spur of necessity, a method of mobilization which has proved to be of distinct value.

49. Nicholsen, C. M.: Angioma of the Liver—Removal—Wound Treated by the Intra-Peritoneal Method, *Interstate M. J.* 9: 427-430, 1902.
50. Noefzel, W.: Extirpation eines Hamangioms der Leber, *Beitr. z. klin. Chir.* 117: 642 646, 1919.
51. Nossen, H.: Zur Lehre von den Angioman der Leber, *Beitr. z. klin. Chir.* 131: 170-179, 1924.
52. Peek, C. H.: Cavernous Haemangioma of Left Lobe of Liver, *Surg. Gynec. & Obst.* 33: 277 280, 1921.
53. Pelligrini, A.: La Resezione del Fegato, Firenze, 1910, L. Niccolai.
54. Perthes: Cited by Thole.
55. Piehler, K.: Ein Fall von Haemangioma hepatis. Heilung durch Extirpation, *Ztschr. f. Heilk.* 24: 250 259, 1903.
56. Podlaha, J.: Haemangioma cavernosum Hepatis, *Bratislavské Lekárské Listy.* 1: 82 87, 1921.
57. Pozzi, G.: Angioma cavernosa del fegato, *Clin. chir.* 8: 625 650, 1932.
58. Ray, B. S.: Large, Cavernous Liver. Report of an Inoperable Case Treated With, *Ann. Surg.* 109: 373-382, 1939.
59. Razemon, P., and Decoulx, P.: Les angiomes du foie, *Rev. de chir.* 77: 188-196, 1939.
60. Richter, J.: Ueber einen Fall von Leberkavernom, *Zentralbl. f. Gynak.* 41: 221-223, 1917.
61. Roggenbau, F.: Zur Kenntnis der Cavernosen Angiom der Leber, *Beitr. z. path. Anat. u. Path.* 49: 313 337, 1910.
62. Rosenthal, J. C.: Extirpation einer Lebergeschwulst, *Deutsche med. Wchnschr.* 23: 54 56, 1897.
63. Rubin, I. C.: Large Pedunculated Angioma of the Liver Reaching Down Into the Pelvis and Causing Obstetric Difficulty, *Am. J. Obst.* 77: 273 276, 1918.
64. Sala, A. M.: Pathological Rarities in Cancer, *Radiol.* 25: 437 439, 1935.
65. Scheleff, N.: Ein operiertes Leberkavernom bei bestehender Schwangerschaft, *Zentralbl. f. Chir.* 66: 1133 1136, 1939.
66. Schulte, J.: Zur Kasuistik der grossen Leberkavernome, *Zentralbl. f. Gynak.* 58: 488 490, 1934.
67. Siebner, M.: Hamangiom der Leber, *Deutsche Ztschr. f. Chir.* 224: 339 343, 1930.
68. Simon, E.: Erfolgreich reseziertes Hemangiokavernom der Leber, *Zentralbl. f. Chir.* 66: 154 158, 1939.
69. Stuchinsky, B. G.: Concerning the Question of Cavernous Hemangiomas of the Liver, *Sovet. vych. gaz.* 39: 891 894, 1935.
70. Tedenat: Excision de tumeurs du foie, *Arch. gen. de med.* 1: 579-590, 1904.
71. Thole, F.: Chirurgie der Lebergeschwulste, *Neue Deutsche Chir.* Stuttgart. 7: 110 115, 1913.
72. Tinker, M. B.: Liver Resection. Case Report and Advantages of Radio cutting, *Ann Surg* 102: 728 741, 1935.
73. Tinker, M. B., and Tinker, M. B., Jr.: Resection of the Liver. Conditions Favorable for Operation; Methods; Experimental Studies, *J. A. M. A.* 112: 2006 2008, 1939.
74. Tumasi, L.: Contributo clinico, operativo e istologico allo studio dell' angioma cavernoso del fegato, *Tumori* 20: 516 533, 1934.
75. Turner, G. G.: A Case in Which an Adenoma Weighing 2 Lb. 3 Oz. Was Successfully Removed from the Liver With Remarks on the Subject of Partial Hepatectomy, *Proc. Roy. Soc. Med. (Sect. Surg.)* 16: 13 16, 1923.
76. Wakeley, C. P. G.: A Large Cavernous Haemangioma of the Left Lobe of the Liver Causing Obstruction to the Cardiac Orifice of the Stomach, *Brit. J. Surg.* 12: 590 592, 1925.
77. Wolfensohn, M. W.: Ueber Leberkavernome, *Norv. chir. Arch.* 32: 527 531, 1925; *abst. Zentralbl. f. Chir.* 53: 1651 1652, 1926.



Fig 2—Incision of parietal peritoneum to open extraperitoneal space

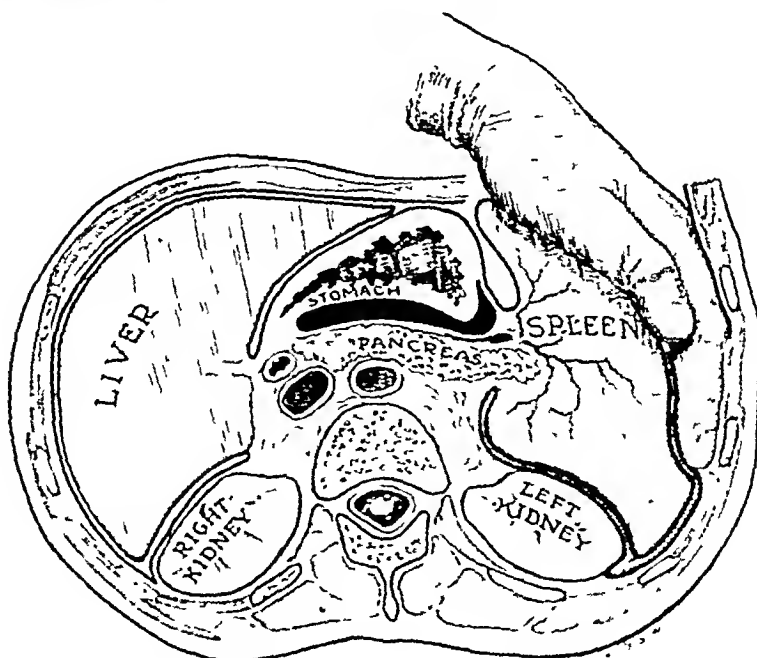


Fig 3—Detachment of parietal peritoneum with the spleen

*Procedure.*—Any one of the incisions commonly used for splenectomy may be employed. My own practice has been to use a long, left mid-rectus hockey-stick incision which has always proved to be adequate. After the abdomen is opened, all accessible adhesions are ligated and divided. The anterior border of the spleen is retracted medially and the lateral margin of the wound is retracted laterally. This develops a fold of parietal peritoneum along the line of the attachment of the adhesions. With knife or scissors the peritoneum is divided just anterior to this fold, the incision extending the full length of the attachment (Fig. 2). This maneuver opens the relatively avascular areolar tissue

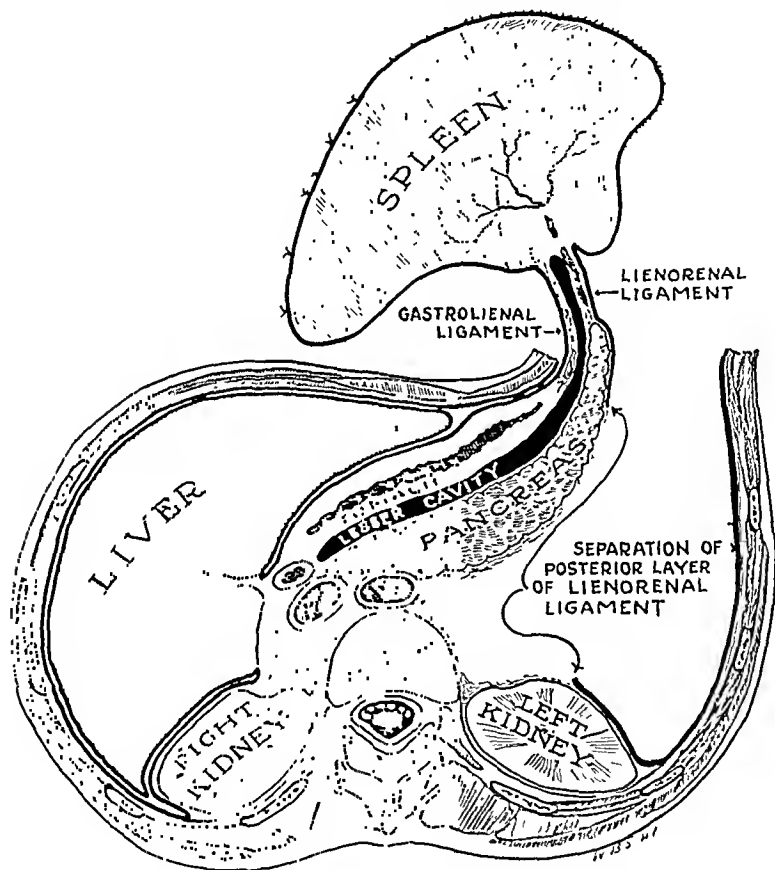


Fig. 1.—Condition after mobilization of spleen by usual method.

plane between the peritoneum and the transversalis fascia. The hand is then inserted into this plane and the dissection is rapidly extended, first posteriorly and then medially (Fig. 3), freeing the spleen from its bed and delivering it onto the abdominal wall still covered by the parietal peritoneum and the posterior layer of the lienorenal ligament (Fig. 4). Most of the blood vessels in the adhesions course within the structures removed with the spleen and consequently are not injured.

than two or three vessels should be included in each group, for centrally located vessels in large masses of tissue are likely to retract through the loop, thus loosening the ligature and permitting it to slip off. The gastrosplenic and the lienorenal ligaments are ligated together (insert. Fig. 4). This is simpler than handling the two separately and has the advantage of preserving the integrity of the lesser peritoneal sac, which prevents adhesion of the posterior surface of the stomach to the raw surface that has resulted from mobilization of the spleen. One must be very careful, of course, to avoid including a portion of the greater curvature of the stomach in the ligatures, an accident which may easily occur if the gastrosplenic ligament is very short. This is most likely to

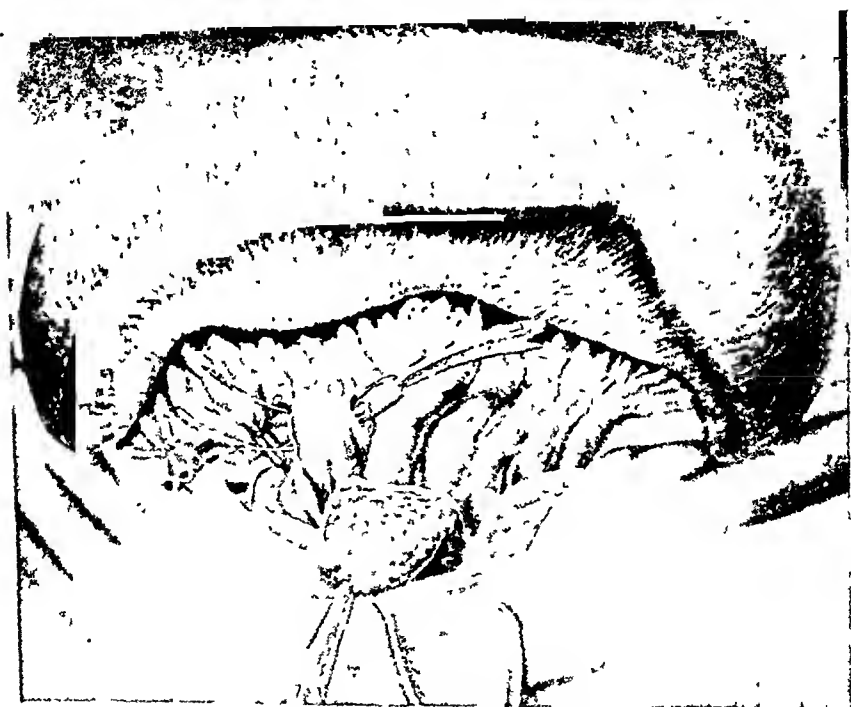


Fig. 5 - Ligature of splenic pedicle. Note that the external surface of the parietal peritoneum is exposed on the surface of the spleen.

occur at the upper margin of the gastrosplenic ligament where the vasa brevia are often extremely short. After the pedicle is carefully inspected for bleeding points and for injury to the pancreas or stomach, it is replaced in the abdominal cavity but is not fixed by sutures. It has been my experience that the ligated pedicle lies naturally in the desired position and that attempts to suture it in place are not only unnecessary but are likely to cause renewed hemorrhage from the pedicle due to puncture of the distended veins by the needle used in suturing. The remaining raw surface, which may be quite extensive, is covered by the omentum, which is turned up over the



There is no danger of laceration of the splenic pulp, for no tension is applied to it, and it is protected from the dissecting fingers by two layers of peritoneum. The procedure is easily and quickly executed, for usually no fibrous bands are encountered. If bleeding from the denuded surface occurs, it is usually moderate in amount and is readily controlled by hot gauze packs. From this point on the operation is carried out in the same manner as if the spleen had been delivered by the conventional technique. The splenic pedicle is now completely exposed on

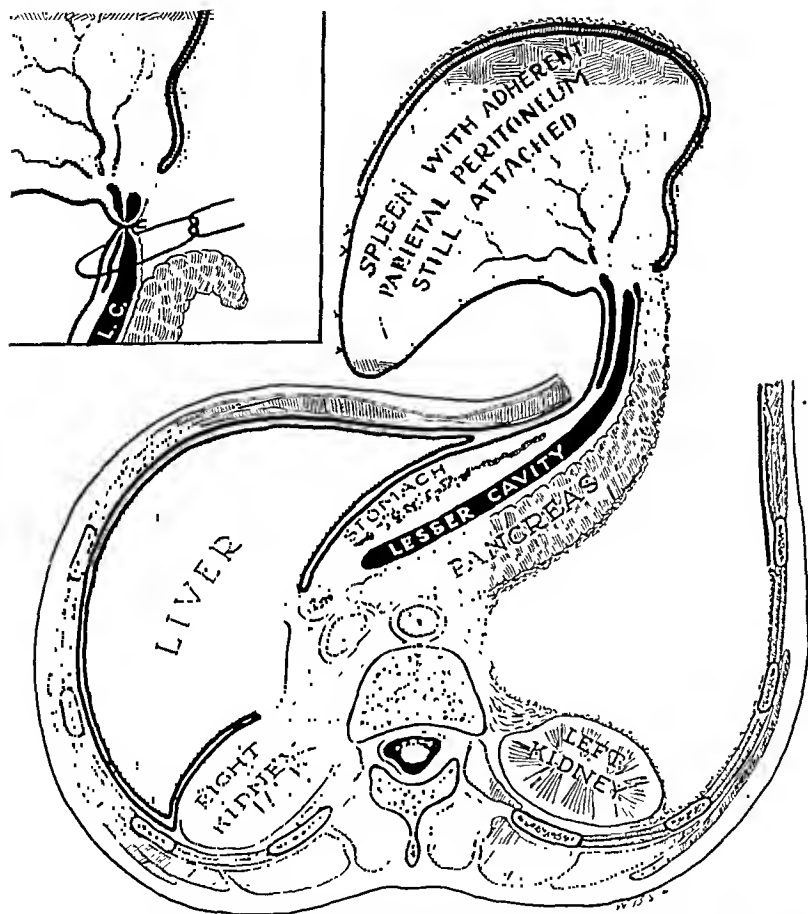


Fig. 4.—Condition after mobilization of spleen by Rives' method. *Insert.* Ligation of gastrosplenic and lienorenal ligaments together, preserving the integrity of the lesser peritoneal cavity.

its posterior aspect. The tail of the pancreas is identified and separated from the pedicle sufficiently to permit free exposure of the vessels. The pedicle is then controlled by a series of heavy catgut ligatures, the large size being selected not for greater strength but to prevent cutting through the very friable veins. It is my practice to pass the ligatures through the pedicle by means of a blunt forceps (Fig. 5). Not more

than two or three vessels should be included in each group, for centrally located vessels in large masses of tissue are likely to retract through the loop, thus loosening the ligature and permitting it to slip off. The gastrosplenic and the lienorenal ligaments are ligated together (insert, Fig. 4). This is simpler than handling the two separately and has the advantage of preserving the integrity of the lesser peritoneal sac, which prevents adhesion of the posterior surface of the stomach to the raw surface that has resulted from mobilization of the spleen. One must be very careful, of course, to avoid including a portion of the greater curvature of the stomach in the ligatures, an accident which may easily occur if the gastrosplenic ligament is very short. This is most likely to

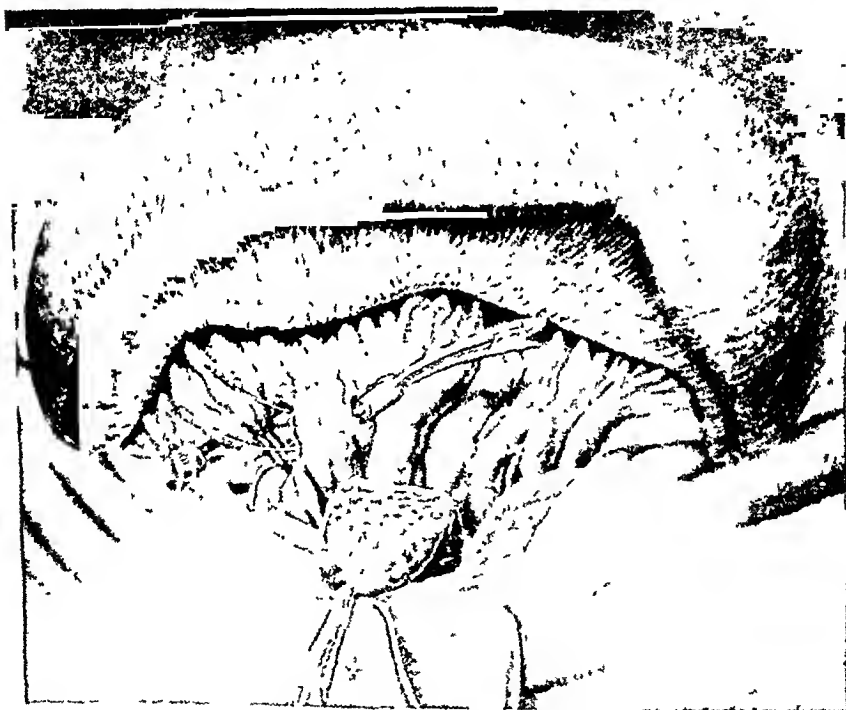


Fig. 5. Ligation of splenic pedicle. Note that the external surface of the parietal peritoneum is exposed on the surface of the spleen.

occur at the upper margin of the gastrosplenic ligament where the vasa brevia are often extremely short. After the pedicle is carefully inspected for bleeding points and for injury to the pancreas or stomach it is replaced in the abdominal cavity but is not fixed by sutures. It has been my experience that the ligated pedicle lies naturally in the desired position and that attempts to suture it in place are not only unnecessary but are likely to cause renewed hemorrhage from the pedicle due to puncture of the distended veins by the needle used in suturing. The remaining raw surface, which may be quite extensive, is covered by the omentum, which is turned up over the

colon and permitted to lie in the splenic fossa. This may be unnecessary because the adhesions that would result if this area were left uncovered would probably not be more extensive than those that occur after a splenectomy during which extensive adhesions have been forcibly torn with the hand. I have seen many examples of the latter that showed no evidence of disturbed gastric function postoperatively, although it is certain that the fundus of the stomach must have become firmly adherent in the region of the denuded surfaces. This portion of the stomach has only slight motility at best and fixation by adhesions probably interferes very little with its function.

#### SUMMARY

A procedure is described that makes splenectomy feasible and comparatively safe in instances in which the operation would be impossible by conventional methods.

## WELCH BACILLUS INFECTIONS ARISING FROM THE STOMACH AND DUODENUM

WILLIAM C. QUINN, M.D., JERE W. LORD, JR., M.D., AND  
LEO J. WADE, M.D., NEW YORK, N. Y.

(From the Departments of Surgery and Pathology of the New York Hospital and  
Cornell University Medical College)

**W**ELCH BACILLUS infections of the peritoneum and abdominal wall have been observed relatively frequently as complications or lesions of the lower intestinal tract.<sup>1</sup> On the contrary, lesions of the stomach and duodenum have rarely given rise to serious infection with the *Bacillus welchii*. A recent case observed on the Surgical Service of the New York Hospital led to a review of the literature for all cases of *Welch bacillus* infections secondary to lesions of, and operations on the stomach and duodenum. Twelve such cases were found in the literature, and to this group two new cases are now added.

A brief review of Case 1 is given here, but a complete description of this case is given in a preceding paper.<sup>1</sup>

**CASE 1.**—G. G. (258992 N. Y. H.), a 52 year-old Spaniard, was admitted to the hospital in February, 1940, with a four months' history of abdominal pain, nausea, vomiting, and later chills and fever. Physical examination revealed an acutely and chronically ill man who showed marked evidence of weight loss. In the epigastrium a tender mass was palpated below a moderately enlarged liver. Following preparation with adequate fluids, an incision and drainage of an abscess of the lesser peritoneum was carried out. Culture of the pus yielded a pure growth of *B. welchii*. Postoperatively the patient developed gas gangrene of the abdominal wall which responded to incision and drainage with adequate débridement of the involved tissue and the local application of zinc peroxide. Sulfanilamide and sulfapyridine were used concomitantly with the above treatment. The gas gangrene of the abdominal wall was under control within four days; however, the patient's course was slow downhill and he expired on the forty-third postoperative day.

**Post-Mortem Examination.**—At post mortem (1942), a mucinous carcinoma of the pancreas with extension into the duodenum, and with perforation and invasion of a diverticulum of the stomach resulting in a perforation into the lesser peritoneal cavity was found. In addition, there was a direct extension of the inflammatory process into the liver with the formation of multiple large abscesses.

A second case of *B. welchii* infection of the peritoneum followed a operation on the stomach.

**CASE 2.**—S. R. (174259 N. Y. H.), a white man, aged 52 years, was admitted to the hospital in July, 1937, with a six months' history of symptoms attributable to a gastric ulcer. Following the usual preoperative preparation, the patient was subjected to a Billroth II type of subtotal gastric resection, and a large gastric ulcer, which had perforated into the body of the pancreas, was removed. On the first day after operation the patient developed signs of gas gangrene of the abdominal

TABLE I  
GAS GANGRENE INFECTIONS IN LESIONS OF STOMACH AND DUODENUM

AUTHOR	YEAR	NO. CASES	AGE	SEX	DIAGNOSIS	OPERATION	WELCH BACILLUS INFECTION†		CULTURES		RESULT
							PERTO-NEUM	ABDOMINAL WALL	PERTO-NEUM	BLOOD STREAM	
Welch and Flexner <sup>2</sup>	1896	1	-*	F	Perforated cancer duodenum	None	I.	O.	<i>B. welchii</i>	-	Death
Flexner <sup>3</sup>	1898	1	-	-	Perforated gastric ulcer	None	I.	O.	<i>B. welchii</i>	-	Death
Pratt and Fulton <sup>4</sup>	1900	1	23	M	Perforated gastric ulcer	Laparotomy	I.	O.	-	-	Death
Page <sup>5</sup>	1900	1	32	M	Perforated gastric ulcer	None	I.	O.	<i>B. welchii</i>	<i>B. welchii</i>	Death
Welch <sup>6</sup>	1900	1	-	-	Perforated gastric ulcer	-	I.	-	<i>B. welchii</i>	-	Death
Welch <sup>6</sup>	1900	1	35	M	Perforated gastric ulcer	-	I.	-	<i>B. welchii</i>	-	Death
Learmonth <sup>7</sup>	1921	1	35	M	Perforated gastric ulcer	Resection of ulcer	I.	O.	-	-	Death
Dayton <sup>8</sup>	1925	1	18	M	Perforated gastric ulcer	None	I.	O.	<i>B. welchii</i>	<i>B. welchii</i>	Death
Douglas <sup>9</sup>	1931	1	-	-	-	Gastric operation	I.	I.	<i>B. welchii</i>	-	Death
Plath <sup>10</sup>	1931	1	31	M	Perforated gastric ulcer	Laparotomy	I.	O.	-	-	Death
Flynn <sup>11</sup>	1936	1	-	-	Carcinoma of stomach	Gastric resection	I.	O.	<i>B. welchii</i>	-	Death
Elavson, Erb, and Gilbert <sup>12</sup>	1937	1	-	-	Peptic ulcer	Gastric resection	-	I.	-	-	Recovery

\* - Not stated.

† I. Presence of infection; O. Absence of infection

gas in the peritoneal cavity and large amounts of pus and pancreatic juice escaping through the wound. *B. welchii*, *B. coli*, and enterococci were recovered on culture on two occasions. The patient's course was rapidly downhill and death occurred on the fourth postoperative day.

*Post Mortem Examination*—At post mortem (8987) a fistulous opening in the center of the wound was found to communicate with a localized abscess; on more extensive investigation this abscess was found to be only one of several collections of pus in the peritoneal cavity, cultures of which grew *B. welchii* and *B. coli*. Careful inspection and gentle pressure on the lines of suture of the gastroenterostomy caused the escape of gastrointestinal contents. The loops of bowel were loosely held together by fibrinous adhesions. There were focal areas of fat necrosis of the pancreas.

#### DISCUSSION

Table I summarizes 12 cases from the literature in which gas bacillus peritonitis or gas gangrene of the abdominal wall have been major complications in lesions of the stomach and duodenum. Nine of these cases had spontaneous perforations, while in 3 the complication occurred as a result of gastric surgery.

There undoubtedly have been many other cases which never have been reported in the literature, but the fact that such infections are so few is not surprising, cultures taken from the stomach or duodenum rarely show *B. welchii*; whereas, these organisms are common inhabitants of the lower portion of the small intestine and of the entire large intestine.<sup>17</sup>

Welch bacillus infections arising from the stomach and duodenum are almost universally fatal. In the 12 cases reviewed above, recovery is reported in only 1 case, the case of Elason, Eib, and Gilbert. In their case infection of the abdominal wall followed resection of a peptic ulcer, but no details are given as to the pathologic process or the therapy.

Treatment of the underlying Welch bacillus peritonitis conforms to the usual therapy for generalized peritonitis, in addition gas bacillus antiserum and one of the sulfonamide derivatives should be used. If there is an associated gas gangrene of the abdominal wall, we believe that in addition to the above therapy, adequate incision and drainage, débridement and the use of zinc peroxide locally according to the technique of Meloney and Johnson<sup>18</sup> should be carried out.

-----

4. Pratt, F., and Fulton, J.: Report of Cases in Which *Bacillus Aerogenes* Capsulates Was Found, Boston M. & S. J. 142: 599, 1900.
5. Page, C.: Case of Perforating Gastric Ulcer With Infection by the *Bacillus Aerogenes* Capsulates; With a Synopsis of the Literature on Infection by This Organism, Canad. Lancet 33: 497, 1900.
6. Welch, W.: Morbid Conditions Caused by *Bacillus Aerogenes* Capsulatum, Bull. Johns Hopkins Hosp. 11: 195, 1900.
7. Learmonth, J.: A Case of Metastatic Gas Gangrene, Lancet 2: 648, 1924.
8. Dayton, W.: Gas *Bacillus* Infection With Perforated Peptic Ulcer, Boston M. & S. J. 193: 507, 1925.
9. Douglas, J.: Discussion of Jennings: Relation of Welch *Bacillus* to Appendicitis and Its Complications, Ann. Surg. 93: 942, 1931.
10. Plath, W.: Ein weiterer Fall von Gasperitonitis, Zentralbl. f. Chir. 61: 1878, 1934.
11. Rhodes, R.: Abdominal Gas *Bacillus* Catastrophes, Ann. Surg. 103: 804, 1936.
12. Eliason, E., Erb, W., and Gilbert, P.: The *Clostridium Welchii* and Associated Organisms, Surg., Gynec. & Obst. 64: 1005, 1937.
13. Simonds, J. P.: Studies in *Bacillus Welchii*, With Special Reference to Classification and to Its Relation to Diarrhea, Monograph of Rockefeller Inst. for Med. Research No. 5, September, 1915.
14. Meleney, F., and Johnson, B.: Prophylactic and Active Treatment of Surgical Infection With Zinc Peroxide, Surg., Gynec. & Obst. 64: 387, 1937.

## GAS GANGRENE OF THE ABDOMINAL WALL

WILLIAM C. QUINN, M.D., JERE W. LORD, JR., M.D., AND  
LEO J. WADE, M.D., NEW YORK, N. Y.

(From the Departments of Surgery and Pathology of the New York Hospital and Cornell University Medical College)

A SERIOUS and much dreaded complication in surgery of the gastrointestinal and biliary tracts is gas gangrene of the abdominal wall. Fortunately this is a relatively infrequent complication and occurs less often after operations on the stomach and duodenum than after those involving the lower intestinal tract. We have recently had the opportunity to study a moderately extensive *Bacillus welchii* infection of the abdominal wall which followed operative intervention for perforations of the stomach and duodenum. The rarity of this condition and the result of therapy in our case, we believe, justify reporting it in some detail.

CASE 1.—G. G. (258992 N. Y. H.), a 50 year-old Spaniard, was admitted to the Surgical Service of the New York Hospital on Feb. 22, 1940, complaining of malaise, abdominal pain, nausea, and vomiting.

*Present Illness.*—Four months before admission the patient first noted epigastric pain of low intensity occurring in short paroxysmal attacks, and two weeks later experienced a chill followed by fever, severe epigastric pain, nausea, and vomiting. He was hospitalized at that time in another hospital, where a moderate anemia and melena were noted, but because of negative gastrointestinal x ray studies, he was discharged without treatment. The abdominal pain which was dull and radiated laterally into the upper quadrants and which was associated with nausea and vomiting continued during the following two months. Anorexia, obstipation, daily fever, loss of weight, and several shaking chills were prominent features during the two months preceding admission.

*Physical Examination.*—The patient was a thin man who gave unmistakable evidence of considerable loss of weight and appeared both chronically and acutely ill. There was relative dullness to percussion over the right chest below the fifth rib posteriorly and in the axilla with diminution of breath sounds and of tactile fremitus over the same area. The epigastrium appeared full and palpation revealed an exquisitely tender mass in that region. The edge of the liver extended two fingerbreadths below the costal margin in the right midclavicular line and was very tender to pressure.

*Laboratory Findings.*—While the urine on admission was found to contain a moderate amount of albumin, with occasional erythrocytes, polymorphonuclear leucocytes and granular casts, subsequent specimens were clear. The hemoglobin was 11.9 Gm. per 100 cc., red blood cells, 4.7 million per centimeter; white blood cells, 23,500, platelet index, 15; plasma prothrombin, 52 per cent of normal; blood culture, negative.

*Course and Treatment.*—Following adequate administration of parenteral fluids, the laparotomy was performed through a right rectus incision on the third day



4. Pratt, F., and Fulton, J.: Report of Cases in Which *Bacillus Aerogenes Capsulatus* Was Found, *Boston M. & S. J.* 142: 599, 1900.
5. Page, C.: Case of Perforating Gastric Ulcer With Infection by the *Bacillus Aerogenes Capsulatus*; With a Synopsis of the Literature on Infection by This Organism, *Canad. Lancet* 33: 497, 1900.
6. Welch, W.: Morbid Conditions Caused by *Bacillus Aerogenes Capsulatus*, *Bull. Johns Hopkins Hosp.* 11: 195, 1900.
7. Learmonth, J.: A Case of Metastatic Gas Gangrene, *Lancet* 2: 648, 1924.
8. Dayton, W.: Gas *Bacillus* Infection With Perforated Peptic Ulcer, *Boston M. & S. J.* 193: 507, 1925.
9. Douglas, J.: Discussion of Jennings: Relation of Welch *Bacillus* to Appendicitis and Its Complications, *Ann. Surg.* 93: 942, 1931.
10. Plath, W.: Ein weiterer Fall von Gasperitonitis, *Zentralbl. f. Chir.* 61: 1878, 1934.
11. Rhodes, R.: Abdominal Gas *Bacillus* Catastrophes, *Ann. Surg.* 103: 804, 1936.
12. Eliason, E., Erb, W., and Gilbert, P.: The *Clostridium Welchii* and Associated Organisms, *Surg., Gynec. & Obst.* 64: 1005, 1937.
13. Simonds, J. P.: Studies in *Bacillus Welchii*, With Special Reference to Classification and to Its Relation to Diarrhea, Monograph of Rockefeller Inst. for Med. Research No. 5, September, 1915.
14. Meleney, F., and Johnson, B.: Prophylactic and Active Treatment of Surgical Infection With Zinc Peroxide, *Surg., Gynec. & Obst.* 64: 387, 1937.

carcinoma, obviously of pancreatic origin. The stomach wall was invaded only at the tip of the diverticulum-like pocket. No tumor cells were found in the liver, but there was a massive destruction of hepatic cells with abscess formation. The portal areas which were extensively infiltrated by plasma cells and lymphocytes showed no inflammation of the biliary ducts while the liver cells contained large quantities of yellow pigment. No evidence of gas gangrene was present in sections of skin and muscle taken from the edges of the wound.

*Diagnosis.*—Mucinous carcinoma of the pancreas with advanced fibrosis; extension of carcinoma into the ampulla of Vater, into the duodenum with perforation, and into the lesser peritoneal cavity; invasion of the tip of a diverticulum-like pocket of the stomach by tumor with perforation into the lesser peritoneal cavity; localized peritonitis with extension of inflammatory process into the liver; formation of multiple large abscesses and massive necrosis of the liver; wounds of laparotomy for drainage of lesser peritoneal cavity with sinus tract into the liver and lesser peritoneal cavity; granulating wounds of abdominal and thoracic wall (*B. welchii* infection of abdominal wall); jaundice.

In 1934 Orr<sup>1</sup> collected all reported cases of gas gangrene of the abdominal wall and found only 18 which he considered acceptable; to these he added 3 cases of his own, all of which were secondary to operations on the intestine and in all of which the patients died. In addition to Orr's series, 1 other case was found reported by Douglas in 1931.<sup>2</sup> Since Orr's report 30 additional cases have been described in the literature, bringing the total to 52. Table I gives a summary of the pertinent data concerning these 52 cases.

Besides the case of *B. welchii* infection described at length above, there have been three cases of gas gangrene of the abdominal wall at the New York Hospital in the past eight years. The histories of the three additional cases are as follows:

after admission and approximately 200 c.c. of pale greenish gray purulent material was drained from an abscess of the lesser peritoneum. The wound was closed around drains with through-and-through silver wire sutures.

Following operation the patient became jaundiced and developed a bronchopneumonia of the left lower lobe which was treated with sulfanilamide and sulfapyridine from the second to the seventh postoperative days. The wound continued to drain moderate amounts of pus which, like that drained from the abscess, yielded a pure culture of *B. welchii*. On the fifth postoperative day a diffuse erythema of the skin over the upper abdomen and lower thorax appeared, the area involved being extremely tender and crepitant. Counterincisions were made at the lateral and superior borders of the inflamed area and the wound was laid open, exposing the liver and the transverse colon. Local applications of zinc peroxide, as recommended by Meleney and Johnson,<sup>18</sup> were used and within four days there was marked improvement in the appearance of the skin of the abdominal wall with decrease in redness, tenderness, and crepitation. No recurrence or spread of the infection occurred, although the wound itself continued to drain pus containing *B. welchii*. In spite of the improvement in the abdominal wall infection, the patient's course was slowly but progressively downhill and was characterized by spiking temperature, chills, jaundice, and tenderness over the right lower thorax. Methylenes blue, administered orally, was recovered in the drainage from the wound in less than eight hours. Sulfapyridine on the thirty-sixth to fortieth days after operation had no apparent effect on the condition of the patient, and on the forty-third postoperative day, pus was aspirated from the liver. A small incision into the liver revealed a large abscess cavity which was drained, but this procedure was of no avail and the patient died within three hours.

*Post-mortem Examination.*—The autopsy (9942) was performed two hours after death. In the epigastrium and right hypochondrium, a large granulating area surrounded by normal skin was present. A small ostium, from which purulent material could be expressed, lay in the center of the granulating wound and communicated with a sinus tract which extended 9 or 10 cm. into the liver. The peritoneal cavity contained 500 c.c. of clear, bile stained fluid. The transverse colon, stomach, gall bladder, and liver were loosely adherent to the anterior abdominal wall and to each other, while the peritoneal surfaces elsewhere were smooth and shining. The liver was large (2,500 Gm.), fluctuant and its external surface was pale red brown and covered by fine fibrous adhesions. The sinus tract extended into the substance of the liver where it was in communication with another tract which extended into the lesser peritoneal cavity. In communication with these tracts were many areas in which the liver substance was completely destroyed and replaced by abscesses containing very foul green pus (*B. lactis aerogenes*, *B. welchii* and nonhemolytic *Streptococcus zymogenes*). The biliary ducts were patent and there was no evidence of thrombophlebitis of the portal vein. The pancreas was replaced by alternating areas of gray mucinous material and extremely hard tumor mass. Direct extension of the tumor tissue into the ampulla of Vater and the adjacent duodenal wall had brought about a perforation 1.5 cm. in diameter just superior to the papilla without causing obstruction to the flow of bile. The tumor also extended upward into the lesser peritoneal cavity where there was a localized accumulation of the same mucinous material and pus (*B. coli communis*, *B. pyocyaneus*, *B. welchii*, nonhemolytic *Str. zymogenes*). A small diverticulum like pocket on the lesser curvature of the stomach was perforated and extended into the abscess of the lesser peritoneal sac. Thus, the stomach, duodenum, and liver were in communication with the abscess of the lesser peritoneal cavity; through the sinus tract in the liver, the abscess communicated with the abdominal wall.

*Microscopic Examination.*—Sections of the pancreas contained focal nests of apparently normal tissue, but most of the parenchyma was replaced by numerous

Tumors of rectum	Resection and enterostomy		Death
	Appendectomy and drainage	Incisions and drainage	
anginous appendix	Drainage	Incision and drainage	Recovery
apical abscess	Cholecystostomy	Incision and drainage	Recovery
ento cholecystitis	Cholecystectomy and appendectomy	Incision and drainage	Death
chronic cholecystitis	Enterostomy	Incision and drainage	Death
astinal obstruction	Appendectomy and drainage	Incision and drainage, antitoxin	Recovery
ento appendicitis	Enterostomy	Incision and drainage	Recovery
astinal obstruction	Cholecystostomy	Incision and drainage, antitoxin	Death
ento cholecystitis	Enterostomy	Incision and drainage	Death
astinal obstruction	Cholecystostomy, appendectomy	Antitoxin	Recovery
ento cholecystitis	Cholecystectomy	Incision and drainage, antitoxin	Recovery
ento cholecystitis	Cholecystectomy	Incision and drainage, antitoxin	Death
tronic cholecystitis	Enterostomy	—	Death
astinal obstruction	Appendectomy	Antitoxin	Recovery
tronic appendicitis	Drainage	Antitoxin	Recovery
peritoneal abscess	Appendectomy, drainage	Antitoxin	Death
ingenuous appendix, with perforation	Cecostomy	Incision and drainage, zinc peroxide	Recovery
—	Gastric resection	—	Recovery
ptic ulcer	Gall bladder surgery (type not stated)	—	—
ate appendicitis	Appendectomy	Incision and drainage, hydrogen peroxide irrigation	Death
—	—	—	Death
—	—	—	Death
perforated appendix	Appendectomy	Antitoxin	Death
uwer of colon, obstruction	Cecostomy	Incision and drainage, antitoxin	Recovery
uwer of colon, obstruction	Cecostomy	Incision and drainage	Recovery
peritoneal abscess	Drainage	Antitoxin	Death
facute appendicitis	Appendectomy and drainage	Antitoxin	Death

TABLE I  
GAS GANGRENE OF ABDOMINAL WALL IN LESIONS OF INTESTINES

AUTHOR	DATE	CASES	NO.	DIAGNOSIS	OPERATION	THERAPY	RESULT
Ochsner and Schmidt	1925	1		Appendical abscess	Appendectomy with drainage	Hydrogen peroxide and Dakin's irrigations	Recovery
Butler	1926	2		1 Appendical abscess 2 Intestinal obstruction	Appendectomy with drainage Cecostomy and lysis adhesions	Multiple incisions and drainage Dakin's irrigations	Recovery Death
L. Murphy	1928	1		Appendical abscess	Drainage	Antitoxin	Death
Shearer	1929	1		Gangrenous appendix	Appendectomy	—*	Death
Butler and Block	1930	2		1 Intestinal obstruction 2 Strangulated ventral hernia	Enterostomy Enterostomy	Antitoxin	Recovery
Falkoff	1930	7		1. Chronic appendicitis 2 Inguinal hernia 3 Intestinal obstruction 4 Intestinal obstruction 5. Acute appendicitis	Appendectomy Hernioplasty Cecostomy Colostomy Appendectomy	Incision and drainage, antitoxin, Dakin's irrigations Antitoxin	Death Recovery Death Death Recovery
Dougherty	1931	2		6. Intestinal obstruction 7. Inguinal hernia	Ileostomy Hernioplasty, appendectomy	None Incision and drainage, Flamine percolation None	Death Recovery
King	1931	1		1. Appendical abscess	Gastric operation Drainage abscess	Flamine irrigations, antitoxin	Death Recovery
Myuncolo	1932	1		Appendicitis	Appendectomy	Antitoxin	Recovery
Pravert	1933	1		Appendical abscess	Appendectomy	Antitoxin	Recovery
Orri	1933	3		1. Appendical abscess Intestinal obstruction 2 Femoral hernia, strangulated	Drainage Drainage, enterostomy Re section, enterostomy	Multiple incisions and drainage	Death Death Death
Kelly	1933	1		3. Intestinal obstruction Strangulated hernia	Enterostomy Operation (type not indicated)	— Antitoxin	Death Death

\*—Not stated.

†At operation a perforation at site of obstruction with generalized peritonitis was found.

CASE 4.—H. Y. (83455 N. Y. H.), a 42-year-old white woman, was admitted to the hospital complaining of cramplike abdominal pain, fever, and weakness.

*Past History.*—In 1935, following a five-day history of obstipation, abdominal cramplike pain, and distention, the patient was admitted to the hospital where an obstructing carcinoma of the sigmoid was diagnosed and removed following preliminary colostomy. An end-to-end anastomosis of the colon was carried out.

*Present Illness.*—The patient remained well until August, 1940, when she was admitted with the history of increasing constipation, abdominal cramplike pain, and weakness for two months.

*Physical Examination.*—This revealed a chronically and acutely ill woman who had a hard, tender mass in the left lower quadrant extending from the left mid-axillary line to the middle of the abdomen.

*Laboratory Findings.*—Hemoglobin, 4.9 Gm.; red blood cells, 2.5; and white blood cells, 24,700.

*Course and Treatment.*—On the seventh hospital day an exquisitely tender, erythematous area developed in the left groin. Following the application of hot wet dressings, an incision released 10 c.c. of foul-smelling pus containing gas bubbles. Culture of the pus revealed *B. welchii*, *B. coli*, and a beta-hemolytic streptococcus. Within the next two days the infection spread rapidly to invade the abdominal wall, extending to the midline, to the costal margin, to the left flank, and down to the middle of the left thigh. Crepitation, marked tenderness, and a pinkish red color of the skin were prominent features. The patient was taken to the operating room where multiple incisions were carried down to the deep fascia which was found to be undergoing liquefaction. A point of perforation was found which extended to the tumor mass in the region of the descending colon. Postoperatively the wound was treated with hourly irrigations of hydrogen peroxide through Dakin's tubes during the day and each night with zinc peroxide dressings. Within seven days the wounds were entirely clean and there was no further spread of the infection. However, the patient's general course was downhill and she died on the twenty first postoperative day.

*Post mortem Examination.*—(10103 N. Y. H.), a recurrent carcinoma of the pelvic colon was found with extensive necrosis and generalized fibrinopurulent peritonitis. There was a moderate degree of fatty degeneration of the liver.

#### DISCUSSION

Although Welch bacillus infection of the abdominal wall may complicate any operative procedure, it most commonly follows surgical intervention for suppurative appendicitis or for intestinal obstruction. In

the intestines were freed and an enterostomy carried out. The enterostomy tube began to function ten hours after operation and the patient passed fecal material by rectum. Eleven hours after operation the temperature rose to 40.1° C per rectum with a comparable rise in pulse rate. Examination of the operative wound revealed extensive gangrene of the edges with marked tenderness and crepitation. Smears and cultures revealed the presence of *B. welchii*, *B. coli*, *B. lactis aerogenes* and enterococci. The abdomen was markedly distended and diffusely tender. Débridement of the abdominal wall was followed by irrigation of the wound with hydrogen peroxide; prontosil was administered intramuscularly and intravenously. The patient's temperature rose to 41.8° C and in spite of therapy she died in coma sixty hours after operation.

*Post mortem Examination*—The examination (9014 N. Y. H.), two hours after death, revealed everted, necrotic borders of the wound with a fibrinopurulent exudate at its base and 100 c.c. of thin, fibrinopurulent fluid in the peritoneal cavity with loops of bowel loosely adherent to one another. In the jejunum, ileum, and ascending colon were many areas of submucosal hemorrhage and edema, while the mucosa of the colon was thick and velvety. An area of ulceration in the jejunum had a necrotic center which extended into the muscularis. The inflammatory process involved the entire bowel wall including the serosa.

CASE 3.—C A (225746 N. Y. H.), a 72 year old man, was admitted to the Surgical Service of the New York Hospital complaining of pain in the abdomen, cramplike and worse in the right lower quadrant, of two weeks' duration. Moderate anorexia and increased fatigability had been noted but there had been no change in bowel habit.

*Physical Examination*—This revealed a dome shaped abdomen in which loud borborygmi could be heard with each bout of cramplike pain, in the right lower quadrant there was a hard, round, immobile mass which was not tender. On rectal examination a firm mass could be felt over the promontory of the sigmoid and the prostate was approximately three times its usual size.

*Course and Treatment*—A flat plate of the abdomen gave evidence of marked distention of the intestine and stomach, and x-ray examination following barium enema showed an obstructive lesion with an irregular filling defect of the sigmoid. On the second hospital day a laparotomy was performed through a right McBurney incision and an abscess was found containing fecal as well as purulent material. Two perforations of the bowel, one of the ileum and the other of the cecum, connected with the abscess. The hard wall at the site of perforation was biopsied and found to be carcinoma. The abscess pocket was drained. On the second postoperative day the borders of the wound were indurated, crepitant, and tender, and culture of the wound revealed *B. welchii* and numerous other organisms. The lesion spread rapidly, involving the entire trunk as high as the midthorax, and the left thigh down to the knee. The temperature remained between 39 and 40° C per rectum and the patient expired on the fourth postoperative day.

*Post mortem Examination*—(9670 N. Y. H.), a deep purplish red discoloration of the skin with induration and crepitus extended from the midthorax to 5 cm. below the left patella, and *B. welchii*, *B. coli*, *Staphylococcus aureus*, and fusiform bacilli were cultured from the lesion of the abdominal wall. The cecum, ileum, sigmoid, colon, and urinary bladder were all firmly adherent to one another and there were two perforations in the wall of the bowel just proximal and distal to the ileocecal valve. The adjacent wall was thickened and infiltrated by tumor cells. The perforations were in direct communication with a localized peritoneal abscess which, in turn, was draining freely through the abdominal wall. In the sigmoid colon was a cauliflower growth 3 cm. in diameter, the surface of which was ulcerated, forming a craterlike depression which had perforated at 1 cm. in continuity with the lesions of the ileocecal region. *B. welchii* and *B. coli* were cultured from the heart's blood.

Longaere and Honold<sup>30</sup> recently have compared the relative value of sulfanilamide, sulfapyridine, sulfathiazole, and sulfamethyl-thiazol in experimental gas gangrene in guinea pigs, and made two significant observations: (1) that in no instance would any of these chemotherapeutic agents protect the animal completely when a moderately large inoculation of a strain of *Clostridium welchii* was injected into the thigh muscles, but that there was slight prolongation of life and this was noted particularly in those animals treated with sulfathiazole and sulfamethylthiazole; (2) that the pathologic changes in the muscle of the animals treated with the latter two drugs were much less advanced, both in intensity and in the extent of the spread, than in the sulfanilamide and sulfapyridine treated animals. Swan<sup>31</sup> reported on the highly successful therapeutic results obtained in a series of cases of frank gas gangrene and others with wounds infected with anaerobic gas-forming organisms by the combined use of antigas gangrene serum and sulfanilamide. This author felt that both agents were of value and that they should be used concomitantly. Wilson<sup>32</sup> stated that in compound fractures of the extremities due to war injuries, sulfathiazole by mouth and the same agent applied directly to the wound after adequate débridement and in association with emasegment in plaster practically eliminated the complication of gas gangrene.

Local x-ray therapy has been successfully employed by Kelly<sup>33</sup> and his findings have been confirmed by several other workers, but the method has not been generally accepted and none of our cases has been treated in this manner.

Local therapy with zinc peroxide was first reported by Meleney and Johnson<sup>34</sup> in 1937; they treated successfully one case of gas gangrene of the abdominal wall. Pearse<sup>35</sup> found zinc peroxide effective in the treatment of a *B. welchii* infection of an open wound which had failed to respond to treatment with x-ray and sulfanilamide. Johnson and Meleney<sup>34</sup> have demonstrated the effectiveness of zinc peroxide against the vegetative forms of *B. welchii* in vitro, but the spores were found to be relatively resistant. They also present evidence of the inactivation of the hemotoxin elaborated by the bacilli by zinc peroxide.

The first case described in this communication (G.G.) was given sulfapyridine and sulfanilamide from the second to the seventh postoperative days, and in spite of this therapy a moderately severe gas gangrene developed. After adequate counterincisions were made and the wound laid open, zinc peroxide therapy was instituted and within five days the infection was well under control. We believe the value of zinc peroxide in this instance is above question while the effect, if any, of the sulfanilamide and sulfapyridine is not clear. It is possible that they may have helped delay the onset or reduced the intensity of the infection, although certainly they were incapable of controlling the infection.

Another recent case of ours (Case 4) supports the efficacy of zinc peroxide in the treatment of these infections. Other than adequate wide-



Table II we have listed in the relative order of their occurrences the surgical procedures which have been followed by gas gangrene of the abdominal wall in 48 of the 52 reported cases.

Although gas gangrene of the abdominal wall is such an infrequent complication of gastrointestinal surgery, the mortality is high, 60 per cent in the collected cases, which makes it extremely desirable to discover effective therapeutic measures for its treatment. Early recognition by the surgeon of this complication is essential. The onset of infection usually is manifested within thirty-six to seventy-two hours after operation, but this period may vary from a few hours to several days, depending largely on the virulence of the organism and the resistance of the patient.

The disease usually begins with an abrupt rise in pulse rate out of proportion to the temperature. There is every evidence of toxicity with general malaise, extreme prostration, restlessness, and perhaps, coma. This is associated with a moderate leucocytosis and usually with a rapid onset of secondary anemia. Marked increase of pain in the wound is often a prominent feature.

Locally the wound may reveal swelling, edema, redness, and especially acute tenderness. The skin at the margin of the wound becomes red, then dusky, progressing to an extremely dark color and finally to total gangrene. The often described sweetish, acid, or "mousy" odor may be noted. Pressure on the margin of the wound produces a sero-sanguineous exudate in which bubbles of gas may be seen. Palpation of the surrounding tissues may produce a definite sense of crepitus. Smears taken from the exudate will almost invariably reveal numerous large gram-positive bacilli, and finally, anaerobic cultures lead to a positive diagnosis.

Four therapeutic agents have been suggested, two of which are systemic and two local. Gas bacillus antitoxin is said to reduce the mortality significantly but as yet there has not been sufficient experience at the New York Hospital to warrant any conclusions as to its value. Sulfanilamide was first used in gas gangrene of the extremities by Bohleman<sup>26</sup> in three patients, all of whom recovered. Sadusk and Manahan<sup>27</sup> reported two instances of *B. welchii* infection following abortion which were successfully treated with sulfanilamide. Bliss and Long<sup>28</sup> state that sulfanilamide has a bacteriostatic effect in experimental *B. welchii* infection in mice. Stephenson and Rosa<sup>29</sup> have compared the therapeutic value of sulfanilamide and sulfapyridine with that of *B. welchii* antitoxin in experimental infection in mice. They concluded that sulfapyridine and sulfanilamide were slightly more effective than the antitoxin when infection was produced by intraperitoneal injection of the Welch bacillus, while sulfanilamide and sulfapyridine were of little or no value when an intramuscular injection of a lethal dose of Welch bacilli was employed. The antitoxin, however, prevented death in all such animals.

24. Pérard, A.: Muscular Gangrene of Appendiceal Origin, *J. Internat. Coll. Surg.* 2: 147, 1939.
25. Breslin, F. J.: Gas Bacillus Infection of the Abdominal Wall in Appendicitis, *Ann. J. Surg.* 49: 501, 1940.
26. Bohlsman, H.: Gas Gangrene Treated With Sulfanilamide, *J. A. M. A.* 109: 251, 1937.
27. Sadusk, J., and Manahan, D.: Sulfanilamide for Puerperal Infections Due to Clostridium Welchii, *J. A. M. A.* 113: 14, 1939.
28. Bliss, E., and Long, P.: Mode of Action of Sulphanilamide, *J. A. M. A.* 109: 1524, 1937.
29. Stephenson, D., and Rosa, H.: The Chemotherapy of Clostridium Welchii Type A and Clostridium Septique Infections in Mice, *Brit. M. J.* 1: 471, 1940.
30. Longacre, A., and Honold, E.: Sulfanilamide, Sulfathiazole and Sulfamethylthiazol in Experimental Gas Gangrene in Guinea Pigs, *Proc. Soc. Exper. Biol. & Med.* 46: 9, 1941.
31. Swan, R. H.: Treatment of Gas Gangrene, *Brit. M. J.* 2: 97, 1940.
32. Wilson, P.: Lecture to Medical Students at Cornell University Medical College, 1941.
33. Pearce, H.: In discussion of Meleney, F., and Harvey, H.: *Ann. Surg.* 110: 1067, 1939.
34. Johnson, B., and Meleney, F.: The Anti-septic Action of Zinc Peroxide on Certain Surgical Anaerobic, Aerobic, and Microaerophilic Bacteria, *Ann. Surg.* 109: 881, 1939.

spread incisions with débridement and drainage and irrigations with hydrogen peroxide, zinc peroxide was the only agent used. The rapid and complete control of the infection was more remarkable in view of the fact that no chemotherapeutic agent or gas gangrene antitoxin was employed.

It would seem advisable to treat any case of gas gangrene involving the abdominal wall with the local application of zinc peroxide according to the technique described by Meleney and Johnson, following the establishment of adequate surgical drainage and débridement. In view of the recent reports from England of the successful prophylaxis and treatment of gas gangrene by the combined use of gas gangrene antitoxin and chemotherapeutic agents, we feel that the gas gangrene antitoxin in combination with adequate amounts of sulfathiazole should supplement the local treatment.

#### REFERENCES

1. Orr, T. G.: Gas Bacillus Infection of the Abdominal Wall, *J. A. M. A.* 102: 2081, 1934.
2. Douglas, J.: Discussion of Jenning: Relation of Welch Bacillus to Appendicitis and Its Complications, *Ann. Surg.* 93: 942, 1931.
3. Ochsner, A., and Schmidt, E. R.: Gas Bacillus Infection Originating in a Gangrenous Appendix, *S. Clin. North America* 5: 911, 1925.
4. Butler, D.: Postoperative Gas Bacillus Infection of Abdominal Wall, *Ann. Surg.* 84: 841, 1926.
5. Lamprecht, H.: Gasbrand bei Appendizitis, *Arch. f. klin. Chir.* 150: 328, 1928.
6. Shearer, J.: Gas Gangrene of the Abdominal Wall Following Gangrenous Appendicitis, *Ann. Surg.* 90: 1114, 1929.
7. Butler, E., and Rhodes, G.: Infection of the Abdominal Wall With *B. Welchii* Following Enterostomy for Bowel Obstruction, *Calif. & West. Med.* 32: 248, 1930.
8. Eckhoff, N.: Gas Gangrene in Civil Surgery, *Brit. J. Surg.* 18: 38, 1930.
9. King, W.: Gas Bacillus Infection in Civil Life, *Am. J. Surg.* 14: 460, 1931.
10. Miyamoto, M.: "Gas Edema" of the Abdominal Wall as a Very Rare Complication of Appendectomy, *Taiwan Igakkai Zasshi* 31: 23, 1932.
11. Traver, M.: Gas Bacillus Infection Complicating Appendicitis, *New York State J. Med.* 33: 946, 1933.
12. Kelly, J. F.: The X-ray as an Aid in the Treatment of Gas Gangrene, *Radiol.* 20: 296, 1933.
13. Nason, L., and Starr, A.: Gas Bacillus Infection Complicating Laparotomy, *Arch. Surg.* 29: 546, 1934.
14. Gamble, H. A.: Emphysematous Gangrene of the Abdominal Wall, *Am. J. Surg.* 28: 389, 1935.
15. Carothers, R.: In discussion of Gamble, H. A.: *Am. J. Surg.* 28: 389, 1935.
16. Howe, B. E.: Report of a Case of Gas Bacillus Infection Occurring in a Wound Following an Operation for Chronic Appendicitis, *New England J. Med.* 215: 871, 1936.
17. Johnson, W.: Gas Gangrene Infections Following Appendectomy, *Am. J. Surg.* 33: 141, 1936.
18. Meleney, F., and Johnson, B.: Prophylactic and Active Treatment of Surgical Infections With Zinc Peroxide, *Surg., Gynec. & Obst.* 64: 387, 1937.
19. Eliason, E., Erb, W., and Gilbert, P.: The Clostridium Welchii and Associated Organisms, *Surg., Gynec. & Obst.* 64: 1005, 1937.
20. Lober, H.: Gasbrand nach Appendizitis, *München. med. Wchenschr.* 85: 1941, 1938.
21. Coleman, E., and Bennett, O.: Personal Experiences With Gas Bacillus Infection, *Am. J. Surg.* 43: 77, 1939.
22. Smith, P., and Zinring, J.: Gas Gangrene of the Abdominal Wall Following Ruptured Gangrenous Appendicitis, *Am. J. Surg.* 39: 351, 1939.
23. Clute, H., and Anglem, T.: Gas Bacillus Infection of the Abdominal Wall, *New England J. Med.* 221: 647, 1939.

24. Pérard, A.: Muscular Gangrene of Appendiceal Origin, *J. Internat. Coll. Surg.* 2: 147, 1939.
25. Breslin, F. J.: Gas Bacillus Infection of the Abdominal Wall in Appendicitis, *Am. J. Surg.* 49: 501, 1940.
26. Bohilman, H.: Gas Gangrene Treated With Sulfanilamide, *J. A. M. A.* 109: 254, 1937.
27. Sadusk, J., and Manahan, D.: Sulfanilamide for Puerperal Infections Due to *Clostridium Welchii*, *J. A. M. A.* 113: 14, 1939.
28. Bliss, E., and Long, P.: Mode of Action of Sulphanilamide, *J. A. M. A.* 109: 1524, 1937.
29. Stephenson, D., and Rosa, H.: The Chemotherapy of *Clostridium Welchii* Type A and *Clostridium Septique* Infections in Mice, *Brit. M. J.* 1: 471, 1940.
30. Longacre, A., and Honold, E.: Sulfanilamide, Sulfathiazole and Sulfamethylthiazol in Experimental Gas Gangrene in Guinea Pigs, *Proc. Soc. Exper. Biol. & Med.* 46: 9, 1941.
31. Swan, R. H.: Treatment of Gas Gangrene, *Brit. M. J.* 2: 97, 1940.
32. Wilson, P.: Lecture to Medical Students at Cornell University Medical College, 1941.
33. Pearse, H.: In discussion of Meleney, F., and Harvey, H.: *Ann. Surg.* 110: 1067, 1939.
34. Johnson, B., and Meleney, F.: The Antiseptic Action of Zinc Peroxide on Certain Surgical Anaerobic, Aerobic, and Microaerophilic Bacteria, *Ann. Surg.* 109: 881, 1939.

## PERITONITIS\*

### III. STUDIES IN PERITONEAL PROTECTION WITH PARTICULAR REFERENCE TO ACTION OF SULFONAMIDE DRUGS IN EXPERIMENTAL PERITONITIS

H. D. HARVEY, M.D., F. L. MELENEY, M.D., AND J. W. R. RENNIE, M.D.,  
NEW YORK, N. Y.

(From the Bacteriological Research Laboratories of the Department of Surgery, Columbia University, College of Physicians and Surgeons, and the Presbyterian Hospital)

IN 1928 we undertook the study of the protection of the peritoneum against infection, having in mind particularly the control of post-operative peritonitis after resections of the colon. We first studied by aerobic and anaerobic methods the peritoneal exudate obtained at operation from 106 human beings with peritonitis,<sup>1</sup> and found that many of the cases without perforation and all the cases with perforation yielded two or more varieties of organisms, if the culture grew at all. Some member of the coli group was nearly always present; next in frequency was some form of intestinal nonhemolytic streptococcus, and third, *Clostridium welchii*. The colon bacillus seemed by far the most important. Somewhat to our surprise the presence of *Cl. welchii* did not add materially to the severity of the infection. We later reported experiments<sup>2</sup> demonstrating that two or more of these species acting together may be more lethal in smaller numbers than when acting alone, as if their action were synergistic.

#### HISTORICAL

The study of peritoneal immunity or protection extends back at least to 1894, when Issaef<sup>3</sup> reported that serum, broth, urine, 2 per cent nucleic acid, and other substances, injected into the peritoneal cavity of guinea pigs, rendered them immune to cholera organisms injected a few days later. The degree of protection was not over fifteen times the dose that killed unprotected controls, but the evidence seemed to be clear that a number of different and unrelated substances would stimulate some protective mechanism within the peritoneal cavity. Klein<sup>4</sup> in 1893 had reported similar nonspecific protection achieved against cholera vibrios by the intraperitoneal injection of various other species. Pfeiffer<sup>5-7</sup> with Issaef also published in 1894 the series of experiments with cholera organisms that demonstrated what later came to be called the Pfeiffer phenomenon, a prompt lysis of the vibrios in the peritoneal cavity of immunized animals. Although this phenomenon was illustrated by the intraperitoneal injection of the cholera vibrios, its relationship to clinical peritonitis was hardly appreciated. In the Cavendish

\*We wish to express our thanks to Miss Daisy Maps and her staff whose care of the dogs made this work possible.

Received for publication, April 21, 1941.

lecture in London in 1904, von Mikuliez<sup>8</sup> reported Miyake's experiments in which intraperitoneal and subcutaneous injections of various substances were shown to give protection against organisms of the colon group or intestinal contents introduced intraperitoneally afterwards. Von Mikuliez had used nucleic acid, neutralized, in 2 per cent strength subcutaneously in fifty-five human beings before abdominal operations, and was pleased with the postoperative course. He explained the beneficial effect by the leucocytosis which the nucleic acid called forth. He tried one intraperitoneal injection of this substance, but it caused so much distress that he did not attempt this route again. Solieri<sup>9</sup> in 1902, after experiments with guinea pigs, tried intraperitoneal injections of saline solution anteoperatively in man. Durham<sup>10</sup> in 1897 recommended the use of streptococcus serum against peritonitis, and Wilkie<sup>11</sup> in 1910 tried convalescent human serum with what he thought was benefit to his patients. Loeffler and Abel<sup>12</sup> in 1896 had demonstrated in guinea pigs specific protection against *Bacillus typhosus* and *Escherichia coli* by intraperitoneal administration of their specific antisera obtained from dogs. Makins and Sargent<sup>13</sup> in 1907 used polyvalent anti-coli horse serum in human beings with peritonitis with questionable benefit.

In 1928, Herrmann<sup>14</sup> revived interest in peritoneal protection by obtaining a certain degree of peritoneal immunity by means of a mixed streptococcus and colon vaccine. Thereafter, Dixon and Barger,<sup>15</sup> and, for a time, Rankin,<sup>16</sup> developed the clinical use of similar vaccines to produce peritoneal protection. Meanwhile Steinberg and Goldblatt,<sup>17</sup> and later Steinberg alone,<sup>18</sup> published their experimental work on dogs, during which they developed their product, baetragen, a composition of gum tragacanth, aleuronat, and the vaccine of a special strain of *E. coli*. This was used intraperitoneally to produce a sterile peritonitis and with it peritoneal immunity. This substance has received favorable comment after a clinical trial by Potter and Collier<sup>19</sup> and Collier and Ransom.<sup>20</sup> Johnson<sup>21</sup> and also Young and Marks<sup>22</sup> have tried and advocated the preoperative use of concentrated amniotic fluid, injected intraperitoneally. Many surgeons, chiefly in Germany, have recommended the use of sera from horses and cattle injected with *E. coli*.

#### THE NEED

The need for new means of preventing postoperative peritonitis in abdominal surgery is still great in spite of advances in surgical technique and pre- and postoperative care during the past decade. At the Presbyterian Hospital in the period 1933 to 1939 inclusive, 316 radical resections were done for carcinoma of the rectum and colon. The postoperative mortality in five of these years lay between 13 and 19 per cent, but two bad years raised the average to 20.3 per cent. This represents the work of the staff as a whole. One member, Charles L. Janssen, who did nearly one-half of the abdominoperineal resections for carcinoma of the rectum, had a mortality rate which was about one-

third that of the staff as a whole, and in the last three years of his life performed 27 of these operations with but 1 death. But the records of a few specially trained and gifted operators do not represent the difficulty experienced by the surgical profession the country over in preventing postoperative deaths after major operations on the intestinal tract.

We have tried to discover what part peritonitis played in this high postoperative death rate but found accurate estimation unobtainable. The diagnosis of postoperative peritonitis is frequently difficult while the patient is yet alive, and even at autopsy the role of any peritonitis found is often hard to appraise. The patients die usually with a complication of lesions. How many of them would have escaped or survived their pneumonia or ileus if they had not also had pus in their peritoneal cavity? A numerical answer cannot be given, but after reviewing the records with care, it is our impression that in one-half of the fatalities, at least, peritonitis was an important cause of death. It is still more difficult to estimate the increase of morbidity from peritonitis among the survivors, but undoubtedly it is a factor of primary importance.

#### CHARACTER OF THE ORGANISMS PRODUCING PERITONITIS

Apart from the rather specialized forms of peritonitis due to single organisms like the gonococcus, the pneumococcus, the hemolytic streptococcus, or the tubercle bacillus, most infections of the peritoneum are produced by inhabitants of the intestinal tract. The organisms most often obtained by culture of intestinal contents are *E. coli*, enterococci, and *Cl. welchii*, the same varieties that we found in our study of the peritoneal fluid of human beings with peritonitis. In 85 per cent of our positive cultures in that study, two or more varieties of organisms were found, illustrating that the infection is usually mixed. We have never obtained a strain of these organisms that was highly virulent for laboratory animals. At times, the virulence of *E. coli* could be enhanced by rapid passage through animals to a point where 10,000 would kill a 20 Gm. mouse, but this was not true of the enterococci or *Cl. welchii*. It was also impossible for us to maintain a constant virulence, so that experiments with the same strain performed on different days could not be compared. Most of the colon forms and the *Cl. welchii* were toxin producers. Some strains of the colon group developed two types of colonies; one, a dark opaque colony, was a toxin producer and relatively virulent; whereas, the other, a light colony, possessed neither of these properties. In addition to the toxins demonstrable in some of the filtrates, there was also a toxin present in the bacterial bodies of cultures that had been killed by heat or formalin. We were never able to evoke any peritoneal protection against injection of these dead bacterial bodies. This may be one reason why we could evoke so little protection against cultures of low virulence, because with them multiples of a lethal dose of living organisms soon approached the lethal dose of killed organisms.

## PROTECTION EXPERIMENTS WITH MICE AND GUINEA PIGS

Our general procedure was to protect the animals, except the controls, by the intraperitoneal injection of various substances, and then test the degree of protection by injecting living bacteria into the peritoneal cavity in varying amounts, and noting how large a dose the protected animals would survive in terms of the doses that would kill the unprotected controls. The infecting organisms were injected as actively growing four- to six-hour cultures of *E. coli*, enterococci, or *Cl. welchii* singly or in combination; or freshly collected human or animal intestinal contents were strained through cotton to eliminate gross particles, and injected; or fresh cultures of intestinal contents were used. Before finally testing each protecting agent, it was necessary to find out in what amount it should be injected, how often, and at what intervals in order to achieve the best results. In general, we found that two injections, given about twenty-four hours and two hours before the bacteria, gave as good results as more numerous injections. The number of organisms injected was estimated by reading a sample from the culture flask by means of the Gates turbidimeter. Dilutions were then made directly from the flask for the largest doses and from them for the smaller doses. No experimental result was accepted unless it could be repeated.

Because of the wide individual variations among the animals in their susceptibility to infection and their response to the protecting agents used, it was necessary to check each dose of organisms by three animals instead of one. In this way, accidental deaths were less likely to confuse the significance of the experiment.

1. *Protection by Means of Living Organisms.*—Clinicians have believed for many years that the peritoneum is more resistant to infection at the time of a second laparotomy than at a first. Whether this is a true, local immunity has never been proved so far as we know. We attempted to study this phenomenon by inoculating guinea pigs intraperitoneally at weekly intervals with gradually increasing doses of living *E. coli*, enterococci, and *Cl. welchii*, the organisms we found most frequently in peritonitis in human beings. Of 16 guinea pigs receiving *E. coli communior*, in only 1 was immunity obtained sufficient to withstand 7.5 minimal lethal doses. Most of the other guinea pigs died of peritonitis during the process. Of 25 animals receiving *Cl. welchii*, only 1 reached an immunity of 12 minimal lethal doses, and it died subsequently of a smaller dose. All the others died of peritonitis or infections of the abdominal wall. Of 31 animals receiving streptococci, only 1 finally withstood 8 minimal lethal doses. Some of the animals received as many as 18 weekly injections. No agglutinins could be found in the animals that did achieve some immunity. It seemed clear from these experiments that immunization by means of living organisms, as we attempted it, at least, was associated with great risk and uncertainty and little hope of practical value.



2. *Protection by Filtrates.*—When intestinal bacteria are grown in a suitable fluid medium, the resulting bacterial emulsion may be centrifuged, and the supernatant portion passed through a Berkefeld filter to yield a clear fluid which is sterile except possibly for filtrable forms. The filtrate may contain among other things bacteriophages, the antivirins described by Besredka, and soluble bacterial products. Its acidity may differ from that of the original medium used. It is, therefore, a complicated fluid of uncertain and variable composition.

We prepared filtrates from various strains of the following: *E. coli*, enterococci, *Cl. welchii*, singly and grown together, human and animal intestinal contents taken from the ileum or parts of the large intestine, and cultures from similar intestinal contents. The filtrates were prepared from cultures grown aerobically or anaerobically. After testing for sterility, the filtrates were injected into guinea pigs or mice which subsequently received living organisms intraperitoneally.

Repeated experiments led to the following deductions. Intraperitoneal injection of filtrates gave better protection than subcutaneous injection. One injection given thirty-six to twenty-four hours before the bacteria, followed by a second injection eight to two hours before the bacteria, gave as good protection as did more frequent doses or doses given at other times. Filtrates administered after the injection of bacteria were of no value. Because the toxicity and potency of the filtrates varied, it was impossible to set a standard dose, but generally 1 c.c. for a 350 Gm. guinea pig and 0.05 c.c. for a 20 Gm. mouse were sufficient. Filtrates prepared from eight-day cultures were not consistently better than those prepared from twenty-four-hour cultures. Filtrates heated to 55° C. were far less potent than unheated. Freshly prepared filtrates were better than those that had been allowed to stand for several days. Rapidity of filtration and the porosity of the filter had no appreciable effect on the value of the filtrate.

It was further found that filtrates prepared from a virulent (dark) colony of *E. coli* almost always gave better protection than did those prepared from other organisms or combinations of organisms or from direct cultures of intestinal contents. Filtrates from avirulent (light) colonies of *E. coli*, on the other hand, were never observed to be potent. These facts held true no matter whether the filtrates were used for protection against *E. coli*, streptococci, *Cl. welchii* in pure culture, or the combination of all three, or intestinal contents or cultures of intestinal contents. We could not show that the *E. coli* filtrate protected better against homologous than against heterologous strains, but we did discover that the degree of protection, measured in minimal lethal doses, was far higher against virulent organisms than against organisms of low virulence.

The degree of protection obtained was often excellent and gave promise of real clinical value, as the following experiment illustrates (Table I).

TABLE I

EXPERIMENT 16.—GUINEA PIGS, WEIGHT 310 TO 370 GM., RECEIVED FILTRATE OF VIRULENT STRAIN OF *E. COLI*, GROWN IN PHOSPHATE BROTH FOR 8 DAYS, FOLLOWED BY LIVING *E. COLI* OF SAME STRAIN.

PIG NO.	FILTRATE INJECTED 12/6/29	FILTRATE INJECTED 12/7/29	ORGANISMS INJECTED 12/8/29	RESULT
1	0.5 c.c.	0.5 c.c.	12 billion	Died
2	0.5 c.c.	0.5 c.c.	6 billion	Lived
3	0.2 c.c.	0.2 c.c.	12 billion	Died
4	0.2 c.c.	0.2 c.c.	6 billion	Lived
5	Control		20 million	Died
6	Control		10 million	Died
7	Control		2 million	Died
8	Control		0.5 million	Died
Result: Protection for 12,000 minimal lethal doses, or more.				

Later experiments, however, showed that a degree of protection comparable to this could be obtained only against the one organism that could be brought to a relatively low numerical minimal lethal dose, namely *E. coli*, and then only when the strain of *E. coli* protected against actually was virulent. As no strains were encountered that were virulent for animals when first obtained, until after repeated animal passage, we feared that the following experiment more truly represented the degree of protection that might be obtained clinically in human beings.

TABLE II

EXPERIMENT 62.—MICE 18 TO 22 GM. VARIOUS FILTRATES USED AS PROTECTING AGENTS AGAINST CULTURE OF *E. COLI*, ENTEROCOCCI, AND *CL. WELCHII* FROM PATIENT T. EACH MOUSE EXCEPT CONTROLS RECEIVED 0.05 C.C. OF DESIGNATED FILTRATE 26 HR. AND 2 HR. BEFORE INJECTION OF ORGANISMS

DOSE OF COMBINED ORGANISMS	FILTRATE (OLD) OF COMBINED <i>COLI</i> , ENTEROCOCCI, AND <i>WELCHII</i> (PATIENT T)	FILTRATE (NEW) OF COMBINED <i>COLI</i> , ENTEROCOCCI, AND <i>WELCHII</i> (PATIENT T)	FILTRATE (NEW) OF COMBINED <i>COLI</i> , ENTEROCOCCI, AND <i>WELCHII</i> (PATIENT L)	FILTRATE (NEW) OF STOOL CULTURE (PATIENT L)
10 billion	Died	Died	Died	Died
1 billion	Died	Died	Died	Died
100 million	Died	Lived	Lived	Lived
10 million	Lived	Lived	Lived	Lived
1 million	Lived	Lived	Lived	Lived
100 thousand	Lived	Lived	Lived	Lived
10 thousand				
CONTROL				
NO PROTECTION				
100 million	Died			
10 million	Lived			
1 million	Lived			
100 thousand	Lived			
10 thousand	Lived			

Result: One minimal lethal dose protection shown for three of the filtrates, no protection shown for the old filtrate.

The experiments with filtrates forced us to conclude that while against virulent strains of *E. coli* good protection could be demonstrated, very little protection could be obtained against organisms whose virulence had not been artificially enhanced by animal passage. Furthermore, we

found that filtrates had the disadvantage of great variability in toxicity and potency, and that they degenerated rapidly. We therefore abandoned them.

3. *Protection With Sera*.—We tried first a horse serum prepared by a commercial laboratory from *E. coli* filtrates that we supplied. While, at first, samples of these sera injected intraperitoneally as prophylaxis against intestinal organisms gave promise of good protection, later tests did not confirm this. After several weeks of trial, this method of producing a potent serum was abandoned.

In our own laboratory, we obtained sera from rabbits that were injected over a period of several weeks intravenously with increasing doses of vaccines and filtrates of *E. coli*, streptococci, and *Cl. welchii*, singly and in combinations. The sera that by agglutination tests appeared to be potent against their antigens were then tested for their ability to protect mice or guinea pigs against infection by various intestinal organisms. As was to be expected from the work with filtrates, by far the best protection we were able to demonstrate was that afforded by the sera from rabbits which had been injected with *E. coli* vaccine (with or without *E. coli* filtrate) when used against virulent *E. coli*. The sera were given intraperitoneally approximately twenty-four hours and two hours before the organisms. Serum given after the organisms were injected did not appear to give much protection. Normal serum consistently gave little or no protection against any organisms and was abandoned as a control.

Experiment 38, which is shown in Table III, illustrates the results obtained. The serum used in this experiment was obtained after the injection of rabbits with *E. coli* vaccine alone. The intestinal contents were obtained from a mouse, emulsified in broth, and the cloudy supernatant fluid pipetted off for use. Similar results were obtained when intestinal contents from guinea pigs were used.

In summary, concerning the serum work, it may be said that while we did not test the sera as extensively as we did the filtrates, the protection afforded by both was roughly of the same degree. The sera, if potent, seemed less toxic and more reliable than the filtrates. To be effective, they had to be given prophylactically. The more virulent the culture, the greater their degree of protection in terms of minimal lethal doses. We made no tests regarding their specificity.

4. *Protection by Vaccines*.—The greatest part of our work was done with vaccines prepared from intestinal organisms singly or in combination. We found no constant difference between heat- and formal-killed preparations. We did not test vaccines made from very young cultures, but generally used eighteen-hour growths. The action of the vaccines was similar to that of the filtrates except that the vaccines were naturally more stable and more consistent in their effects. *E. coli* vaccine consistently gave as good protection as did vaccines of other species, and often better. We could show no better protection against the

TABLE III

EXPERIMENT 38.—MICE 18 TO 22 GM. EACH MOUSE, EXCEPT CONTROLS, RECEIVED 0.25 C.C. OF RABBIT ANTI-COLI VACCINE SERUM 26 HR. AND 3 HR. BEFORE INJECTION OF BACTERIA OR INTESTINAL CONTENTS.

DOSE OF VIRULENT E. COLI	SERUM-PROTECTED MICE	CONTROL, UNPROTECTED MICE
4 billion	Died	
1 billion	Lived	
100 million	Lived	Died
10 million		Died
1 million		Died
DOSE OF MOUSE INTESTINAL CONTENTS EMULSIFIED IN SALINE SOLUTION AND PIPETTED OFF	SERUM-PROTECTED MICE	CONTROL, UNPROTECTED MICE
20.0 c.c. concentrated	Died	
10.0 c.c. concentrated	Died	
2.0 c.c.	Died	Died
1.0 c.c.		Died
0.5 c.c.		Died
0.1 c.c.		Lived

Result: Protection by serum amounting to at least 1,000 minimal lethal doses against the virulent strain of *E. coli*, but less than 20 minimal lethal doses against the cloudy supernatant fluid from the intestinal contents.

homologous strains of *E. coli* than against heterologous. The degree of protection again in general rose with the virulence of the organism against which protection was aimed. Against emulsions of intestinal contents, or cultures of intestinal contents, the protection rarely exceeded ten minimal lethal doses, but against a relatively virulent strain of *E. coli* the protection reached into the thousands of minimal lethal doses.

5. *Protection by Substances Other Than the Above.*—We had by this time satisfied ourselves by experiments many times repeated that we knew how much protection could be obtained by injections of living organisms, filtrates, vaccines, and sera derived from the common intestinal organisms. In attempting to find a substance better than any of these, we entered upon a series of experiments in which we compared the protecting capacity of the derivatives just mentioned with the protection afforded by various other substances. In order to conduct comparative tests of this kind, it is most important to be sure that the protecting substances which are being compared are employed in the manner best suited to each. This means careful study of each new substance employed, to be certain that it is being correctly used. Obviously one cannot test all possible substances, or even test all possible ways of using one substance. As evidence for the statements we are about to make, we must point chiefly to the fact that we used over 7,000 animals in our various tests and attempted many variations in the use of our protecting agents in the hope that we would not overlook any manner of dosage that would give the best protection. In addition to the vaccines, sera, and filtrates of *E. coli*, enterococci, and *Cl. welchii*, we tested two brands of German commercial *E. coli* sera, *Staphylococcus aureus* vaccine, *E. coli* bacteriophage of our own production, amniotic fluid

concentrate, Borgen's *E. coli* and enterococcus vaccine, coli vaccine in gum tragacanth of our own make, Steinberg's bactragen, aleuronat, New York Board of Health typhoid vaccine, several pneumococcus vaccines, crude lecithin added to coli vaccine, broth, saline solution, acetic acid of varying strengths, aleuronat and starch mixture, sulfanilamide. We found several of these substances that gave as good protection as did coli vaccine but none that gave better in mice and guinea pigs.

#### NATURE OF THE PROTECTION OBTAINED

When any substance is injected into the peritoneal cavity, there is a reaction by the body which results in peritonitis. The degree of reaction varies with the nature and amount of the injected substance, and also with the reacting properties of the individual who receives the injection. It is not practical to inject enough of a bland substance like saline solution to produce a marked peritonitis. Therefore in order to obtain a strong peritoneal reaction, more irritating substances must be used. Shortly after the injection, the animal may show evidence of pain. There is an increase of peritoneal fluid. There may be within fifteen minutes a transient increase of small round cells in the peritoneal fluid, and shortly thereafter the large mononuclear cells, found in normal peritoneal fluid, are replaced by a great relative and actual increase of polymorphonuclear leucocytes. The only exception to this reaction that we found was when a large dose of virulent living organisms, such as *Cl. welchii*, was injected, in which case the animal often died without ever achieving a leucocytic response. Usually, however, as the leucocytes increase, the peritoneal fluid becomes thicker, clumps of fibrin appear containing cells and bacteria (if they have been injected), until, within about three or four hours, large, deeply staining mononuclear cells begin to appear in appreciable numbers, which we take to be young macrophages. By six hours after injection, the macrophages are clearly to be identified. Under favorable circumstances, phagocytosis is well under way by this time, both by leucocytes and macrophages. The proportion of macrophages continues to rise as degeneration of the various types of cells proceeds. At the end of five or six days, the peritoneal fluid may be hardly distinguishable from normal. Although the local peritoneal and subperitoneal phenomena are so pronounced that one is tempted to call the whole reaction local, it is obvious that the remainder of the body must also take part in it.

In general, the degree of immunity we obtained was highest when the peritoneal reaction was most intense. In fact, animals that were made so sick by the preliminary injection that they appeared about to die often withstood the largest doses of infecting organisms. Such intense peritoneal reactions could be produced by nonspecific substances like aleuronat and starch mixture, or by bacterial products like *E. coli* vaccine, and the protection afforded by each was in general the same. We therefore look on this protection as a function of the intensity of

the peritoneal reaction, short of actually causing the death of the animal, and also as a nonspecific phenomenon, whose efficacy against any infecting organisms is independent of the substance used to produce it. An exception to this statement is the protection afforded by *E. coli* bacteriophage, which was effective against its own homologous strain of *E. coli*, but ineffective against other strains of coli or against other organisms. The protection obtained by drugs may also be of a different nature.

Experiment 176 (Table IV) supports the idea of nonspecificity, because if the protection were specific, one would expect the homologous vaccine in each of the two series to protect better than the heterologous. This was not the case.

TABLE IV

EXPERIMENT 176.—MICE 18 TO 22 Gm. TWO SETS OF MICE RECEIVED 50 MILLION *E. COLI* VACCINE INTRAPERITONEALLY 24 HR. BEFORE INJECTION OF LIVING BACTERIA. TWO OTHER SETS OF MICE RECEIVED 500 MILLION VACCINE MADE FROM STRAIN OF HEMOLYTIC *STREPTOCOCCI* OF RELATIVELY LOW VIRULENCE, AT SAME TIME. ONE OF EACH SET RECEIVED HOMOLOGOUS COLON ORGANISMS, AND ONE HOMOLOGOUS *STREPTOCOCCI*.

DOSE OF ORGANISMS	<i>COLI</i> VACCINE VS. <i>COLI</i> ORGANISMS	<i>STREPTOCOCCUS</i> VACCINE VS. <i>COLI</i> ORGANISMS	<i>COLI</i> VACCINE VS. <i>STREPTOCOCCUS</i> ORGANISMS	<i>STREPTOCOCCUS</i> VACCINE VS. <i>STREPTOCOCCUS</i> ORGANISMS
400 million	Died	Died	Died	Died
400 million	Died	Died	Died	Died
250 million	Died	Died	Died	Died
250 million	Died	Died	Died	Died
100 million	Died	Died	Died	Died
100 million	Died	Died	Lived	Died
50 million	Died	Died	Lived	Lived
50 million	Lived	Lived	Lived	Lived
10 million	Lived	Lived	Lived	Lived
10 million	Lived	Lived	Lived	Lived
DOSE OF ORGANISMS	UNPROTECTED CONTROLS VS. <i>COLI</i>	UNPROTECTED CONTROLS VS. <i>STREPTOCOCCI</i>		
10 million	Died	Died		
10 million	Died	Died		
1 million	Died	Died		
1 million	Died	Lived		
100 thousand	Died	Lived		
100 thousand	Died	Lived		

*Result:* The vaccines in each case protected almost equally well against the heterologous organism as they did against the homologous strain. The fact that the colon strain was more virulent than the streptococci does not alter this conclusion.

#### SUMMARY OF THE EXPERIMENTS WITH MICE AND GUINEA PIGS

1. Any substance injected into the peritoneal cavity of mice or guinea pigs produces a peritoneal reaction.
2. If the reaction is severe enough, it is accompanied by a measurable degree of immunity against subsequent intraperitoneal injection of various organisms.

concentrate, Barger's *E. coli* and enterococcus vaccine, coli vaccine in gum tragacanth of our own make, Steinberg's bactragen, aleuronat, New York Board of Health typhoid vaccine, several pneumococcus vaccines, crude lecithin added to coli vaccine, broth, saline solution, acetic acid of varying strengths, aleuronat and starch mixture, sulfanilamide. We found several of these substances that gave as good protection as did coli vaccine but none that gave better in mice and guinea pigs.

#### NATURE OF THE PROTECTION OBTAINED

When any substance is injected into the peritoneal cavity, there is a reaction by the body which results in peritonitis. The degree of reaction varies with the nature and amount of the injected substance, and also with the reacting properties of the individual who receives the injection. It is not practical to inject enough of a bland substance like saline solution to produce a marked peritonitis. Therefore in order to obtain a strong peritoneal reaction, more irritating substances must be used. Shortly after the injection, the animal may show evidence of pain. There is an increase of peritoneal fluid. There may be within fifteen minutes a transient increase of small round cells in the peritoneal fluid, and shortly thereafter the large mononuclear cells, found in normal peritoneal fluid, are replaced by a great relative and actual increase of polymorphonuclear leucocytes. The only exception to this reaction that we found was when a large dose of virulent living organisms, such as *Cl. welchii*, was injected, in which case the animal often died without ever achieving a leucocytic response. Usually, however, as the leucocytes increase, the peritoneal fluid becomes thicker, clumps of fibrin appear containing cells and bacteria (if they have been injected), until, within about three or four hours, large, deeply staining mononuclear cells begin to appear in appreciable numbers, which we take to be young macrophages. By six hours after injection, the macrophages are clearly to be identified. Under favorable circumstances, phagocytosis is well under way by this time, both by leucocytes and macrophages. The proportion of macrophages continues to rise as degeneration of the various types of cells proceeds. At the end of five or six days, the peritoneal fluid may be hardly distinguishable from normal. Although the local peritoneal and subperitoneal phenomena are so pronounced that one is tempted to call the whole reaction local, it is obvious that the remainder of the body must also take part in it.

In general, the degree of immunity we obtained was highest when the peritoneal reaction was most intense. In fact, animals that were made so sick by the preliminary injection that they appeared about to die often withstood the largest doses of infecting organisms. Such intense peritoneal reactions could be produced by nonspecific substances like aleuronat and starch mixture, or by bacterial products like *E. coli* vaccine, and the protection afforded by each was in general the same. We therefore look on this protection as a function of the intensity of

a generalized, not merely diffuse, peritonitis was present in all dogs that we autopsied in the acute stage. The appendix tip itself usually became a swollen, dark red, gangrenous mass. The peritoneal fluid was usually at first intensely bloody and present in large amounts. Each culture made from it grew *E. coli*, enterococci, and *Cl. welchii* and at least three other strains of variable nature. The peritonitis was therefore the result of a mixed infection. The control dogs, and those inadequately protected, usually died within forty-eight hours although there were some that died later, and an occasional survivor. The after-treatment consisted of morphine as indicated for pain, water to drink and food later if the dog survived long enough. In addition, the specific treatment being tested was given. When drugs were injected through the T-tube in water, an equal quantity of water was given by the same route to the controls. This never exceeded 150 c.c. in twenty-four hours.

Almost all of the survivors were autopsied three to five weeks after operation. Those sacrificed early showed a well-isolated abscess containing the tape that was used to tie off the appendix tip. After four or five weeks even this had often disappeared. The remainder of the peritoneal cavity showed little evidence of the severe infection which it had suffered.

The results of the experiments were as follows:

*Controls*—No peritoneal protection, and no drugs except morphine for pain. Died in one day, 6; in two days, 4; in three days, 2; in four days, 1; in seven days, 1; survived, 2. Total: 14 died, 2 survived. Percentage of survivors, 12.5 per cent.

*Bactragen*—One ampule, 30 c.c., given intraperitoneally twenty-four hours before operation. Treatment otherwise as for controls. This substance was selected as representative of the group that had been most effective in producing immunity in the guinea pig and mice experiments. It has furthermore been used extensively in dog experiments by Stenberg, and its best method of employment therefore probably ascertained. All the dogs which received it developed large amounts of bloody peritoneal exudate before operation. Died in one day, 1; died in two days, 2; died in three days, 4; died in four days, 1; died in five days, 1; died in eight days, 1; survived, 1. Total: 10 died, 1 survived. Percentage of survivors, 9 per cent.

In addition to the 11 dogs listed above were 2 which disrupted their wounds when they seemed extremely ill, discharged large amounts of pus, and finally recovered. This introduced a factor which makes it unfair to consider them in the series. There were also 2 other dogs which died, 1 under the anesthetic (which no uninjured dog in our experience of several hundred dogs has done), and 1 which was too sick the morning after receiving bactragen to operate upon. The last 2 provide evidence that the injection of bactragen is not without risk to the recipient.



3. The immunity appears to be nonspecific, except in the case of certain substances like bacteriophage in which the protection afforded appears to be due chiefly to its specific bactericidal property.

4. The degree of immunity obtained may reach several thousand minimal lethal doses against relatively virulent organisms, such as strains of *E. coli* whose virulence has been artificially raised. *E. coli*, enterococci, *Cl. welchii*, and other intestinal organisms, as obtained from the intestinal tract or from pus, are in our experience always of low virulence, and against these strains the degree of immunity is usually of the order of ten minimal lethal doses. This is true also of intestinal contents, filtered through cotton.

5. We found no single protecting agent that was of outstanding value.

#### EXPERIMENTS WITH DOGS

We used mice and guinea pigs for the preliminary work just described, because many of the experiments required the use of fifty or more animals the same day. This part of the work was open to two obvious criticisms: first, that the method of producing peritonitis, i.e., by injection of a single dose of organisms, was unlike the method in which it usually arises in human beings, and, secondly, that the nature of the reaction in these small animals makes them unsuitable for experiments that could be interpreted in terms of human beings. We shifted to dogs, not only because of their greater size, but because we could produce in them a lesion that was not unlike acute gangrenous perforated appendicitis with subsequent diffuse peritonitis. The procedure was as follows: The dogs were anesthetized with sodium nembutal given intravenously. After preparing the skin of the abdomen we entered the peritoneal cavity through a right rectus incision a little above and to the right of the umbilicus. The appendix (or cecal appendage) was delivered into the wound, and the blood supply to the distal 4 cm. divided and ligated. A piece of umbilical tape was tied tightly around the appendix just proximal to the distal 4 cm., so as to shut off gross fecal leakage and to make sure that no blood supply reached the tip through the wall of the appendix. The distal 4 cm. was then laid open for its entire length, and the underlying mucosa wiped grossly clean of worms and feces, leaving behind, of course, many organisms on the mucosal surface. A T-tube was then placed into the midportion of the small intestine for enteral administration of drugs, and brought out through a close-fitting separate tract that was carried through subcutaneous tissues for several inches in order to prevent leakage of peritoneal fluid around the tube. The rectus wound was then carefully closed in layers. In spite of all efforts to produce a uniform lesion in this manner, it was of course impossible to do so because of inevitable variation in the nature and number of organisms present in the dogs' appendices. However, the lesion produced was uniform to this degree, that gangrene of the distal 4 cm. of the appendix always resulted, and

of administration was devised. Two of these survived, 2 died with minimal peritonitis but with pneumonia at fifteen days and nineteen days after operation, and 2 died clearly of peritonitis two days after operation.

*Sulfanilamide*.—This was similarly administered by T-tube, except that the doses given were 3.6 Gm. or sometimes 2.4 Gm. The blood levels ran from 9 to 20 mg. per cent.

One died in four days, 1 died in ten days, 2 survived. Percentage of survivors, 50 per cent.

In addition, there were 3 dogs which received the drug by mouth which died in two days, six days, and nine days. It may be that further tests would have shown that this drug was as good as sulfathiazole, but the results so far as we went, even though the sulfanilamide blood levels were higher, were not encouraging.

*Sulfanilamide Intraperitoneally*.—One dog received 6 Gm. about the appendix tip at the close of the operation, 5 received 9 Gm., 1 received 12 Gm., and 1 15 Gm. The blood levels of the dogs receiving 9 Gm. were 8, 16, 24, 34, 36 mg. per cent the morning after operation. By the following morning they had fallen to 1, 5, 4, 14, 20, respectively. Of the five dogs which received 9 Gm., 4 died of peritonitis (2 in three days, 1 in eleven days, 1 in seventeen days). One survived. The dog which received 6 Gm. survived; those which received 12 and 15 Gm. died in two days and three days.

Total: 6 died, 2 survived. Percentage of survival, 25 per cent.

The sulfanilamide intraperitoneally was apparently more beneficial than the sulfathiazole intraperitoneally, though not as effective as either when given and maintained by enteral administration. The appendix in this group of dogs did not become the large soft dark red mass that it did in most of the others. It turned into a relatively dry gray gangrene, nor was the peritoneal fluid as offensive.

*E. coli Vaccine*.—Given intraperitoneally the day before operation. It produced a sterile bloody peritoneal fluid, which on smear was hardly to be distinguished from that produced by bacetragein, but was distinctly less in amount. One dog received 500 billion and died as a result of the anesthetic (cf. Bacetragein), 1 received 250 billion which killed him without operation, 1 received 200 billion and died four days after the operation, 1 received 100 billion and survived. Four others received 100 billion total in two doses given twenty-four and four hours before operation plus 15 c.c. of *E. coli* bacteriophage total in the two doses. One of these died as a result of the injection. The others died within two days of operation.

Total: Died, 7; survived, 1. Survival percentage, 12.5 per cent.

*E. coli Bacteriophage*.—Two dogs received 10 c.c. of bacteriophage intraperitoneally at the end of operation and 5 c.c. intravenously the next morning. Both were dead in two days.

*Sulfathiazole*.—Various methods of administration were tried, but the only one that we found practical in the dogs was the injection of a watery emulsion directly into the small intestine by T-tube. In this way they could not vomit it. They appeared to absorb it at variable rates. We tried sodium sulfathiazole both enterally and by vein, but found that this form of the drug was rapidly absorbed, giving very high blood levels, which soon fell sharply so that a continuous effect was not obtained. We finally came to giving two 5 Gm. doses the day of operation, one immediately and one six hours after operation, and two or three similar doses on subsequent days, depending on the apparent need for it. We seldom continued the drug for more than three days. The blood levels we obtained ranged from 0.5 mg. per cent to 8 mg. per cent, but were usually under 4 mg. per cent. Died in three days, 1; survived, 11. Percentage of survivors, 91.7 per cent.

There were three other dogs which received sulfathiazole while we were experimenting with the dosage and the route of administration of the drug, before we hit upon the T-tube method. Two received the drug in part by mouth and vomited an unknown quantity of it. One of these showed a blood level of zero after receiving 9 Gm. in twenty-four hours. The other showed a blood level of 9 mg. per cent the day of operation, but thereafter received only sodium sulfathiazole by rectum, subcutaneously, and intraperitoneally. These two dogs died in three and two days, respectively. The third dog received chiefly sodium sulfathiazole by T-tube, achieving variable blood levels up to 25 mg. per cent. The drug was stopped on the fourth day as he seemed nearly well, but he failed again after the tenth day and was sacrificed on the thirteenth day. He was found at autopsy to have diffuse peritonitis. As none of these three dogs received the drug in what we later found to be the correct method, we are reporting them separately, only for the sake of completeness. Were they included in the series, the survival rate would be 73 per cent.

*Sulfathiazole Intraperitoneally*.—We gave 5 dogs 10 Gm. of sulfathiazole powder intraperitoneally at the end of the operation, and 1 dog 12 Gm. This amount of powder was placed on and about the tip of the appendix after the usual lesion had been produced and the abdominal wound was ready to be closed.

Died in one day, 4; died in eight days, 1; survived, 1. Total: Died, 5; survived, 1. Percentage of survivors, 16.7 per cent.

*Sulfapyridine*.—This was administered by T-tube into the intestine in the same manner and amount as was the sulfathiazole. The blood levels were about the same.

Died in two days, 3; survived, 5. Percentage of survivors, 62.5 per cent.

One of the 3 that died had extensive pneumonia and perhaps should not be counted in the series. In addition, there were six other dogs that received the drug by mouth or by vein before the T-tube method

monly cause peritonitis in man. We found that several substances injected intraperitoneally twenty-four hours before the organisms would afford a limited immunity. We then took what seemed to be the best of these substances and compared their effect upon peritonitis in dogs with the effect of some of the sulfonamide drugs. The lesion produced in the dogs resembled that encountered in human beings, in that it was a peritonitis caused by a mixed growth of intestinal organisms emanating from a focus of gangrenous cecal appendage. It is significant that pre-operative immunization of the peritoneum had little effect upon this type of lesion. Whereas we cannot express the degree of effectiveness of the sulfonamides in terms of minimal lethal doses, we believe our experiments justify their further trial as preventive and curative agents for peritonitis in man. If there is any advantage in intraperitoneal use of the crystals of these drugs, as opposed to administration by other routes, we failed to demonstrate it. The evidence is rather to the contrary. However, the number of dogs used was not sufficient to show conclusively which route of administration, or even which of the sulfonamide drugs, should be employed in human beings. These problems, we believe, should be solved by trial clinically.

We believe our experiments have shown that there is strong evidence that the sulfonamide drugs, properly selected and administered, will be of use in lowering the death rate from peritonitis. There was also some evidence of benefit from preoperative injection of substances into the peritoneal cavity in the effort to produce peritoneal immunity, but the benefit was slight and definitely less than that afforded by the sulfonamide drugs. There appears to be no benefit to be derived from pre-operative injection that cannot be better obtained from the sulfonamides.

#### CONCLUSIONS

1. Various substances injected into the peritoneal cavity of mice or guinea pigs will produce an immunity to peritonitis caused by subsequent intraperitoneal injection of intestinal organisms.
2. The immunity appears to be nonspecific in nature.
3. The degree of immunity against organisms as obtained from the intestinal tract or from pus in the peritoneal cavity is usually of the order of ten minimal lethal doses. Only against strains of *E. coli*, whose virulence had been artificially enhanced, did the immunity rise to the order of 1,000 minimal lethal doses.
4. In experiments involving over 7,000 animals, no protecting substance of unique value was found. The best protecting agents were the irritative ones, such as the vaccines, potent sera, bacitracin, or aleuronat and starch mixture.
5. In dogs with generalized peritonitis following artificially produced acute gangrenous perforated appendicitis, the immunity afforded by preoperative intraperitoneal injections of the best of the protecting agents was not sufficient to lower the mortality.

## SUMMARY OF EXPERIMENTS WITH DOGS

1. Acute gangrenous perforated appendicitis was produced in dogs, which resulted apparently uniformly in generalized peritonitis.

2. Eighty-seven and one-half per cent of the untreated controls died of peritonitis.

3. Preoperative peritoneal protection afforded by bactragen, *E. coli* vaccine or *E. coli* bacteriophage did not lower the mortality or significantly prolong life.

4. Sulfathiazole placed in the peritoneal cavity in the vicinity of the appendix was of little apparent benefit; sulfanilamide similarly used seemed to have some value in lowering the mortality and in prolonging life.

5. Enteral administration of sulfapyridine, sulfathiazole and, less definitely, of sulfanilamide, was followed by a striking lowering of mortality. In the case of sulfathiazole, the mortality fell to 8.3 per cent, compared to 87.5 per cent for the controls. The mortality with sulfapyridine was 37.5 per cent, with sulfanilamide 50 per cent.

6. The peritonitis in each case cultured was found to be due to a mixture of organisms, among which the varieties commonly found in human peritonitis were predominant; viz., *E. coli*, enterococci, *Cl. welchii*. These results are summarized in Table V.

TABLE V

	TOTAL NO. DOGS	DIED 1 DAY	DIED 2 DAYS	DIED 3 DAYS	DIED 4 DAYS	DIED 5-7 DAYS	DIED 8-14 DAYS	DIED 15-21 DAYS	SURVIVED	DIED	SURVIVED %
Controls	16	6	4	2	1	1			2	14	12.5
Bactragen*	11	1	2	4	1	1	1		1	10	9
Sulfathiazole† (enterally)	12			1					11	1	91.7
Sulfathiazole (intraperi- toneally)	6	4					1		1	5	16.7
Sulfapyridine‡	8		3						5	3	62.5
Sulfanilamide§	4				1		1		2	2	50
Sulfanilamide (intraperi- toneally)	8		1	3			1	1	2	6	25
<i>E. coli</i> vaccine	8	3	3		1				1	7	12.5
Bacteriophage	2		2						0	2	0

\*Two others disrupted wounds, discharged pus and survived, 1 other died from anesthetic, 1 other too sick following bactragen to operate upon.

†Three others received sulfathiazole inadequately. They were the first 3 to receive it, before the proper dose was established. All died, see text.

‡Two other dogs received sulfapyridine by mouth; these survived. Four other dogs received sulfapyridine by vein; 2 of these died on the second day, 2 died on the fifteenth and nineteenth days of pneumonia.

§Three others received drug by mouth, drug not retained. One survived, 2 died on the sixth and ninth days.

## DISCUSSION

In the experiments with mice and guinea pigs we attempted to render the peritoneal cavity immune to infection by the organisms that com-

## EXUDATIVE INTERSTITIAL NEPHRITIS (PYELONEPHRITIS)

E. T. BELL, M.D., MINNEAPOLIS, MINN.

(From the Department of Pathology, University of Minnesota)

**I**NFLAMMATIONS of the interstitial tissues of the kidneys are commonly called pyelonephritis since in the majority of instances both the pelvis and the renal parenchyma are involved. But pyelonephritis is not always an accurate descriptive term since cortical abscesses occur not infrequently without involvement of the pelvis and a mild pyelitis may exist without notable extension into the parenchyma; these conditions may be designated cortical abscesses and pyelitis, respectively.

One objection to the use of the term interstitial nephritis is that this name was formerly applied to the contracted kidneys of chronic glomerulonephritis and primary hypertension because of the secondary condensation of connective tissue about the atrophic tubules. However, the older terminology has been in disuse so long that there will probably be no confusion from the use of this accurately descriptive term.

The most important feature of this group of renal diseases is that they are caused by the lodgement of bacteria in the kidneys. Glomerulonephritis and some of the tubular diseases are caused by toxic substances of bacterial origin, but in exudative interstitial nephritis the bacterial bodies lodge in the kidneys and provoke an inflammatory reaction. The causative organisms may be recovered from the kidney by cultural methods.

### A. CORTICAL ABSCESS

Cortical abscesses often extend into the pelvis and may then be appropriately called pyelonephritis. Three anatomical types of cortical suppuration may be distinguished: viz. multiple small abscesses, earlele, and perinephric abscess.

1 *Multiple small abscesses* are chiefly of anatomical interest since they are usually found in autopsy material in association with staphylococcal bacteremia, and there may have been no direct clinical evidence of their presence. In patients dead of staphylococcal bacteremia it is not uncommon to find multiple small cortical abscesses which have not yet extended to the pelvis. The abscesses vary from microscopic dimensions to a diameter of 1 cm. or more. In sections of such kidneys it may often be determined that the abscesses begin in glomeruli and then extend into the adjacent tubular areas. The bacteria evidently lodge in the glomerular capillaries where they are attacked by polymorphonuclear leucocytes. In the early stages numerous leucocytes pass through the glomerular capillaries and are carried through the

6. In a parallel series of dogs, however, postoperative enteral administration of the sulfonamide drugs, especially sulfathiazole, was followed by a striking lowering of mortality. Intraperitoneal use of these drugs was less effective.

7. On the basis of this evidence we recommend the use of the sulfonamides clinically but do not recommend the use of preoperative injections.

## REFERENCES

1. Meleney, F. L., Harvey, H. D., and Jern, H. Z.: Peritonitis. I. The Correlation of the Bacteriology of the Peritoneal Exudate and the Clinical Course of the Disease in One Hundred and Six Cases of Peritonitis, *Arch. Surg.* 22: 1-66, 1931.
2. Meleney, F. L., Harvey, H. D., Olpp, J., and Zaytzeff-Jern, H.: Peritonitis. II. Synergism of Bacteria Commonly Found in Peritoneal Exudates, *Arch. Surg.* 25: 709-721, 1932.
3. Issaef: Researches Concerning the Artificial Immunity to Cholera, *Ztschr. f. Hygiene* 16: 287-328, 1894.
4. Klein, E.: The Anti-Cholera Vaccination. An Experimental Critique, *Brit. M. J.* 25: 632-634, 1893.
5. Pfeiffer, R.: Further Researches Concerning the Existence of Cholera Immunity and Concerning Specific Bactericidal Processes, *Ztschr. f. Hygiene* 18: 1-16, 1894.
6. Pfeiffer, R., and Issaef: Concerning the Specific Significance of Cholera Immunity, *Ztschr. f. Hygiene* 17: 355-400, 1894.
7. Pfeiffer, R., and Issaef: Concerning the Specificity of Cholera Immunization, *Deutsche Med. Wchnschr.* 13: 305-306, 1894.
8. Von Mikulicz-Radecki, J.: Experiments on the Immunization Against Infection of Operation Wounds Especially of the Peritoneum, *Lancet* pp. 1-4, 1904.
9. Solieri, S.: Experimental Researches on Changes in the Resistance of the Peritoneum to Infection With Bacterium Coli Following the Intraperitoneal Injection of Different Substances and Their Application to the Abdominal Surgery of Man, *Policlin. Roma* 9C: 1-16, 1902.
10. Durham, H. E.: On the Clinical Bearing of Some Experiments on Peritoneal Infection, *Med. Chir. Trans.* 80: 193-204, 1897.
11. Wilkie, D. P. D.: Serum Therapy in Acute Peritoneal Infections, *J. Path. & Bact.* 14: 270-281, 1910.
12. Loeffler, F., and Abel, R.: Concerning the Specific Properties of Immune Bodies in the Blood of Animals Immunized to Typhoid and Colon Bacilli, *Zentralbl. f. Bact.* 19: 51-70, 1896.
13. Makins, G. H., and Sargent, P.: On the Value of Anti-Colon Bacillus Serum, *Tr. Clin. Soc., London* 40: 146-155, 1907.
14. Herrmann, S. F.: Experimental Peritonitis and Peritoneal Immunity, *Arch. Surg.* 18: 2202-2215, 1929.
15. Dixon, C. F., and Bagen, J. A.: Vaccination Preceding Colonic Operations as Protection Against Peritonitis, *New York State J. Med.* 35: 529-532, 1935.
16. Rankin, F. W.: Resection of the Rectum and Recto-Sigmoid by Single or Graded Procedures, *Ann. Surg.* 104: 628-635, 1936.
17. Steinberg, B., and Goldblatt, H.: Protection of the Peritoneum Against Infection, *Surg., Gynec. & Obst.* 57: 15-20, 1933.
18. Steinberg, B.: The Experimental Background and the Clinical Application of the Escherichia coli and Gnm Tragacanth Mixture (Coli-Baetragen) in Prevention of Peritonitis, *Am. J. Clin. Path.* 6: 253-277, 1936.
19. Potter, E. B., and Coller, F. A.: Intraperitoneal Vaccination in Surgery of the Colon, *Ann. Surg.* 101: 886-890, 1935.
20. Coller, F. A., and Ransom, H. K.: The One-Stage Procedure of the Treatment of Carcinoma of the Rectum, *Ann. Surg.* 104: 636-650, 1936.
21. Johnson, H. L., Coonse, K., Hazard, J. B., Foisee, P. S., and Aufranc, O.: Amniotic Fluid Concentrate as an Activator of Peritoneal Immunity, *Surg. Gynec. & Obst.* 62: 171-181, 1936.
22. Young, E. L., Jr., and Marks, G. A.: Pre-operative Preparation of the Peritoneum in Surgery of the Large Intestine, *Surg., Gynec. & Obst.* 59: 610-615, 1934.

nephritis. Pyelonephritis occurs both with and without obstruction of the urinary tract. If simple renal abscesses without pyelitis be excluded, the obstructive type is about twelve times as frequent as the nonobstructive but attracts less attention since the renal symptoms are overshadowed by the major illness responsible for the obstruction.

In our 32,360 autopsies there were 1,229 cases of hydronephrosis of varying degrees of intensity, and 60 per cent of these (744 cases) showed pyelonephritis. In Table I these cases are arranged with re-

TABLE I

BILATERAL AND UNILATERAL HYDRONEPHROSIS SHOWING FREQUENCY OF RENAL INFECTION IN DIFFERENT ETIOLOGICAL GROUPS

	NUMBER		BI- LATERAL	UNI- LATERAL	PER CENT INFECTED
	MALES	FEMALES			
Carcinoma of uterus		143	101	42	37.0
Pregnancy		60	30	30	23.0
Ureteral stricture	51	37	20	68	30.7
Urethral obstruction	37	3	34	6	72.0
Carcinoma of prostate	131		107	24	71.0
Hypertrophy of prostate	319		287	32	83.0
Carcinoma of bladder	76	16	69	23	82.0
Other obstructions of bladder	27	22	26	23	61.0
External ureteral obstructions	57	109	85	81	46.0
Paralytic, spinal cord	77	35	109	3	68.7
Paralytic, congenital	23	6	22	7	17.0
Total	798	431	890	339	60.0

spect to the cause of the hydronephrosis, and the percentage with pyelonephritis in each group. In the same autopsy material there were only 64 cases of pyelonephritis without hydronephrosis.

#### ROUTE OF INFECTION

1. *Ascending Infections.*—It will be noted in Table I that obstructive lesions of the urethra, bladder, and prostate produce infection of the kidneys about twice as frequently as obstruction of the ureters above the bladder. Obstructions which distend the bladder are almost invariably associated with cystitis, the ureteral orifices tend to become dilated and there is opportunity for reflux of infected urine into the ureters. These facts suggest that ascending infection plays an important role in the development of pyelonephritis resulting from obstruction of the lower urinary tract. On the other hand, when the block is in the ureter above the bladder, it is difficult to understand how ascending infection can occur.

Experimentally pyelonephritis may be produced in rabbits by introducing infection into the bladder and then obstructing the urethra; in dogs it may be produced without obstruction by infecting the bladder and cutting the ureteral orifices so that they remain open (Gruber and Rabinovitch).

In low urinary tract infections in man the ureters and the bladder form a common chamber, as the result of dilatation of the ureteral



tubules toward the pelvis. The tubules associated with infected glomeruli are filled with polymorphonuclear leucocytes. It is probable that bacteria are carried in this way through the tubules to the renal pelvis. When the tubule becomes plugged with leucocytes, the infection spreads beyond its lumen into the adjacent tissue. This is the reason we so often see streaks of suppuration extending radially from the apex of the pyramid to the cortex.

A microscopic section through a small abscess shows a central mass of cocci surrounded by a zone of necrosis beyond which is a dense wide zone of polymorphonuclear leucocytes. The central necrosis is caused by the necrotizing toxin liberated by the staphylococci. In abscesses of subacute or chronic course the polymorphonuclear cells may be replaced partly or entirely by macrophages or lymphocytes.

As stated above, multiple small abscesses are found most frequently in cases of frank staphylococcic bacteremia, but they are also frequent in those dead of diabetic coma and are seen occasionally in other diseases in which there was no clinical evidence of renal disease. Apparently these abscesses are caused by *Bacillus coli* and staphylococci and the infection evidently reaches the kidney through the blood stream.

Although no direct evidence is available, it is highly probable that small abscesses may heal leaving as residues only small scars or lymphocytic infiltrations.

2. *Renal Carbuncle*.—Carbuncle refers to a large multilocular honey-combed abscess. Good descriptions have been given by Brady, O'Connor, and Patch. The lesion is much more often unilateral than bilateral. The patient exhibits symptoms of a septic infection with localizing signs in the region of the involved kidney, but there is commonly no pyuria.

Usually an obvious source is demonstrable, a carbuncle, furuncle, or cellulitis of the skin. A few cases follow sore throat. Staphylococci are found in the carbuncle. The infection may break through the renal capsule to form a perinephric abscess.

Brady, who collected ninety-five cases from the literature, recommends drainage rather than nephrectomy.

3. *Perinephric abscess* refers to suppuration about the kidney outside of its capsule. It is widely believed that perinephric abscesses always represent an extension of a cortical abscess through the renal capsule, but Vermooten maintains that they may develop outside the renal capsule and are not extensions of a cortical suppuration. The etiology is the same as that of cortical abscess. Surgical drainage is usually recommended, especially when the kidney is not extensively destroyed.

#### B. PYELONEPHRITIS

The majority of infected kidneys show involvement of both the pelvis and the parenchyma and may be appropriately designated as pyelo-

from 60 to 80 per cent (Cabot, Culver and co-workers, Haslinger, Hellström). The remainder are due chiefly to staphylococci. The authors have not distinguished obstructive and nonobstructive forms in their bacteriologic studies, and we therefore do not know the proportions of colon and staphylococcal infections in the two groups. However, it is clear that in the nonobstructive group, which comprises about 8 per cent of the pyelonephritides, the staphylococci are chiefly responsible since the infection usually originates in a known staphylococcal lesion such as a furuncle or carbuncle (Nesbit). Discrete cortical abscesses are due to staphylococci, but diffuse inflammations are more often caused by colon bacilli. Frequently a colon bacillus infection is superimposed on a staphylococcal inflammation.

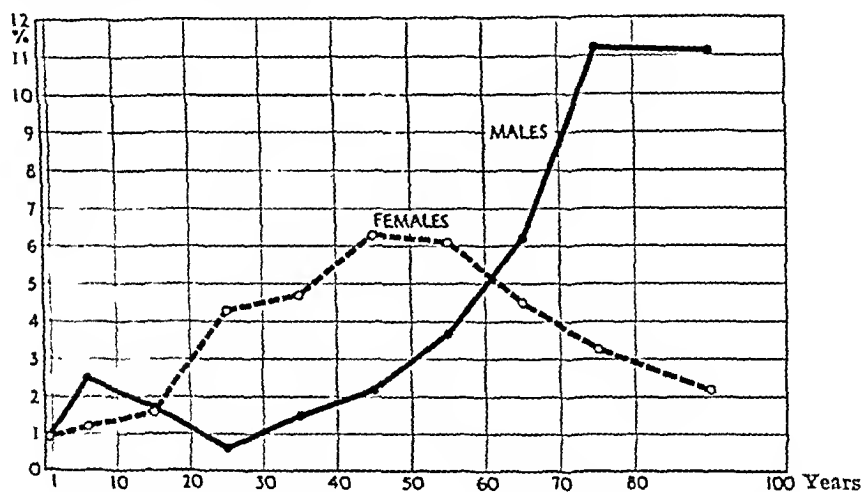


Fig. 1.—Distribution of hydronephrosis in autopsies according to age and sex.

#### A. OBSTRUCTIVE TYPE

*Symptoms.*—In pyelonephritis associated with obstruction the clinical picture is usually dominated by the disease responsible for the hydronephrosis such as hypertrophy of the prostate, carcinoma of the bladder, and carcinoma of the uterus, but evidences of infection (fever, leucocytosis, pain or tenderness in the region of the kidneys, etc.) may be superimposed on those of the major illness.

The age and sex distribution of the obstructive type of pyelonephritis corresponds to that of hydronephrosis (Fig. 1). During the third, fourth, fifth, and sixth decades it predominates in females because of pregnancy and carcinoma of the uterus, but after that time there is a great preponderance in males chiefly because of prostatic disease.

The pyelonephritis of pregnancy exhibits special features. Hydronephrosis of some degree is nearly always present during pregnancy and this predisposes the kidneys to hematogenous infection. About 1

orifices. Upon contraction of the bladder infected urine is forced into the ureters, and the bacteria may be transported to the pelvis of the kidney by mechanical dissemination through the urine, by to-and-fro movements, or by the motility of the organisms; e.g., colon bacilli.

When the infection reaches the renal pelvis, it produces pyelitis, and in the earlier stages a direct extension of the inflammation into the medullary pyramids may be seen. The infection may spread directly from the mucosa into the renal parenchyma or it may reach the parenchyma through minute tears of the mucosa which result from pelvic distention. In retrograde pyelograms it is sometimes noted that the radiopaque substance escapes into the peripelvic tissues (pyelointerstitial or pyelovenous reflux), and it is believed that this mechanism comes into play in obstructive hydronephrosis. In animals substances injected up the ureter under pressure pass directly into the veins (pyelovenous reflux), and the veins of the kidney may be readily injected through the ureter.

In the early stages ascending and hematogenous pyelonephritis may be distinguished by examination of the kidneys, but this distinction can seldom be made in the advanced stages.

2. *Hematogenous Infections*.—Pyelonephritis developing in the absence of urinary obstruction is generally believed to be of hematogenous origin. In the case of ureteral obstructions (Table I) the infection is also presumably hematogenous since none of the factors which favor ascending infection are present. It is possible that the infection reaches the kidney through the blood stream in some cases with low urinary obstruction. It is known that a positive blood culture may frequently be obtained after operations on the lower urinary tract, and even after catheterization (Scott, Young). The urethral chill is attributed to bacteriemia.

It is well established that hydronephrosis predisposes the kidney to hematogenous infection. If the ureter of one kidney of a rabbit be ligatured and staphylococci be injected intravenously after forty-eight hours, it will usually be found that multiple abscesses develop in the obstructed kidney but not in its normal mate. It is therefore easily possible that bacteria from the infected bladder enter the blood stream and thus reach the cortex of the hydronephrotic kidneys.

3. *Lymphogenous Infections*.—A few writers have supported the view that infection spreads from the bladder to the kidney through the periureteral lymphatics (Eisendrath, Sweet and Stewart). The chief evidence in support of this hypothesis is the presence of a lymphocytic exudate in the outer wall of the ureter. This finding is, however, more readily explained as a chronic ureteritis similar to a chronic pyelitis.

#### BACTERIOLOGY

Nearly all writers agree that colon bacilli are responsible for the great majority of infections of the urinary tract, the estimates varying

from 60 to 80 per cent (Cabot, Culver and co-workers, Haslinger, Hellström). The remainder are due chiefly to staphylococci. The authors have not distinguished obstructive and nonobstructive forms in their bacteriologic studies, and we therefore do not know the proportions of colon and staphylococcal infections in the two groups. However, it is clear that in the nonobstructive group, which comprises about 8 per cent of the pyelonephritides, the staphylococci are chiefly responsible since the infection usually originates in a known staphylococcal lesion such as a furuncle or carbuncle (Nesbit). Discrete cortical abscesses are due to staphylococci, but diffuse inflammations are more often caused by colon bacilli. Frequently a colon bacillus infection is superimposed on a staphylococcal inflammation.

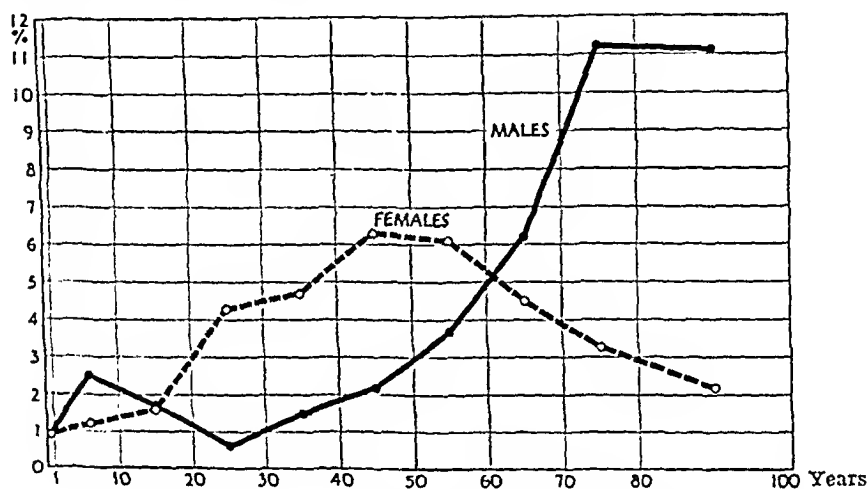


Fig. 1.—Distribution of hydronephrosis in autopsies according to age and sex.

#### A. OBSTRUCTIVE TYPE

**Symptoms.**—In pyelonephritis associated with obstruction the clinical picture is usually dominated by the disease responsible for the hydronephrosis such as hypertrophy of the prostate, carcinoma of the bladder, and carcinoma of the uterus, but evidences of infection (fever, leucocytosis, pain or tenderness in the region of the kidneys, etc.) may be superimposed on those of the major illness.

The age and sex distribution of the obstructive type of pyelonephritis corresponds to that of hydronephrosis (Fig. 1). During the third, fourth, fifth, and sixth decades it predominates in females because of pregnancy and carcinoma of the uterus, but after that time there is a great preponderance in males chiefly because of prostatic disease.

The pyelonephritis of pregnancy exhibits special features. Hydronephrosis of some degree is nearly always present during pregnancy and this predisposes the kidneys to hematogenous infection. About 1

per cent of pregnant women develop pyelitis. In McLane's ante-partum series of 98 cases, 60 developed pyelitis during the third trimester, 35 in the second, and 3 in the first. In 232 cases von Illyés found 145 on the right, 48 on the left, and 39 bilateral. Only a few patients give a history of pyelitis in childhood. The chief symptoms are chills, fever, leucocytosis, renal pain, and pyuria. By means of drainage and chemotherapy most of the patients may be cured before the onset of labor, but about 15 to 20 per cent of the cases result in abortion or premature delivery. The maternal mortality is about 3 per cent.

Pyelonephritis during the puerperal period is somewhat less frequent than during pregnancy and generally develops during the first week. Pyelonephritis occasionally recurs during a subsequent pregnancy, but there is no satisfactory evidence that it causes toxemia. Rarely the pyelonephritis of pregnancy continues as a chronic pyelonephritis, but we have no example of this in our collection.

In the paralytic and congenital types of hydronephrosis the associated pyelonephritis is easily recognized clinically. In all forms of hydronephrosis infection destroys more or less of the renal parenchyma and hastens the onset of uremia.

#### B. NONOBSTRUCTIVE TYPE

This form may be called hematogenous or descending pyelonephritis, and it is what clinicians usually have in mind when they speak of pyelonephritis. As pointed out above, however, the obstructive type is twelve times as frequent as the nonobstructive in autopsy material. There is usually no difficulty in distinguishing the two types at autopsy, but in chronic nonobstructive cases the shrinkage of the cortex may produce some enlargement of the pelvis and an associated inflammation of the ureter may cause a partial mechanical or paralytic obstruction.

1. *Acute Hematogenous Pyelonephritis*.—This lesion blends with cortical abscesses to such an extent that no sharp separation is possible. I have grouped under this heading only the cases in which cortical abscesses were associated with gross involvement of the renal pelvis and have classified all cases of less than four months' duration as acute. There are a large number of cases of cortical abscesses in our autopsies, but there are only 50 good examples of acute pyelonephritis.

The chief symptoms are fever, renal pain and tenderness, dysuria, tenesmus, pyuria, leucocytosis, and anemia. Weiss and Parker found the disease relatively common in early childhood, during pregnancy, and in old age. In children malformations in the urinary tract are a contributory cause, and in older subjects diabetes is often a predisposing influence. The prognosis is usually favorable.

Referring to the 50 fatal cases found in our autopsy records it is noteworthy that there was usually an associated disease, usually of infectious nature, which was largely responsible for death and over-

shadowed to some extent the symptoms referable to the kidneys. For convenience these 50 cases will be divided into four groups with respect to age.

(a) CHILDREN UNDER 1 YEAR OF AGE.—There are 7 cases in this group, 3 males and 4 females; the ages being 1 month, 2, 2, 3, 4, 7, and 9 months, respectively. Two patients had otitis media and meningitis. 1 had mastoiditis, 1 had pharyngitis, and 1 had an initial upper respiratory infection. In the 2 remaining cases there was no disease other than the pyelonephritis. The duration varied from ten to thirty days. The blood pressures were not recorded. At autopsy in each case both kidneys showed cortical abscesses with extensions into the pelvis.

(b) CHILDREN FROM 1 TO 10 YEARS OLD.—There were 4 cases in this group, 3 females and 1 male, the ages being 2, 3, 6, and 8 years, respectively. The duration varied from one to three weeks. The complicating infections in 3 cases were acute osteomyelitis, meningococcal meningitis, and acute enterocolitis, respectively. In the fourth case there was a moderate unilateral hydronephrosis of undetermined cause which may have been the initial site of the infection. The blood pressures were not recorded. At autopsy the kidneys showed bilateral abscesses and suppurative pyelitis.

There is an extensive literature on acute pyelonephritis in children. Prior to 1909 it was generally regarded as a pyelitis on the assumption that the renal parenchyma was not involved. In 1909 Thomson and McDonald reported 25 cases, 21 girls and 4 boys, with 21 recoveries. In 2 autopsies on boys, aged 4 and 7 months, they found cortical suppuration as well as pyelitis. In 1910 Thiemich reported 7 autopsies, in 6 of which there was infection in the renal parenchyma.

Wieland, in 1918, described 45 cases with 4 deaths. There were 35 girls and 10 boys. In nursing infants the sexes were about equal, but all of his patients over 3 years old were girls. The predisposing causes were respiratory and intestinal infections, and *B. coli* was the organism usually found. Chown, in 1927, reported 21 autopsies on children under 2 years of age, all with parenchymal lesions in the kidneys. The sexes were about equal, and *B. coli* was the only organism found. Twelve of the 21 cases had infection outside the kidneys. The disease was bilateral in 12 instances, on the right in 6, and on the left in 2 cases.

It is now generally agreed that the pyelitis of children is pyelonephritis. In most instances it is secondary either to some obvious focus of infection elsewhere or to a respiratory or intestinal infection. The majority of the patients recover, but a few die and a few develop chronic pyelonephritis. Chronicity is favored by any anomaly which prevents drainage of the kidneys. With modern methods of treatment the percentage of recoveries should be notably increased and the duration of the illness shortened.

Wharton, Gray, and Guild made a careful study of 30 girls and young women from 3 to 14 years after acute pyelitis in childhood. One

had severe chronic pyelonephritis, and 16 others had slight but definite abnormalities in the urinary tract but no symptoms. One had a recurrence of pyelitis during pregnancy and another went through pregnancy without difficulty.

(c) **PERSONS FROM 10 TO 40 YEARS OF AGE.**—There are 10 cases in this group, 8 females and 2 males, the ages being 17, 22, 23, 24, 27, 29, 29, 32, 34, and 34 years, respectively. The duration varied from two weeks to two months. The predisposing cause in 4 patients, 1 of whom was a boy 17 years old, was diabetes. In 1 patient the renal infection followed a peritonsillar abscess, and in another it was the outcome of puerperal endometritis. In 1 instance the disease followed an upper respiratory infection. Monocytic leucemia was the cause of 1 death in this group. Apart from the 4 cases of diabetes and the 1 of monocytic leucemia death was apparently due to uremia and this was established by the high blood urea nitrogen in 2 instances (urea nitrogen, 161, 173 mg. per cent). In 2 cases one kidney was removed shortly before death, but the infection continued in the other kidney and uremia developed. The disease was bilateral in each of the 10 cases.

Blood pressures were recorded in 6 of the 10 cases. In 4 patients the highest systolic pressure was 130 mm. Hg. In one the pressure was 148/96, but no kidney tissue was available for microscopic study. In another the pressure ranged from 100/64 to 150/90, and no renal arteriolosclerosis was found.

(d) **PERSONS OVER 40 YEARS OF AGE.**—There are 29 cases in this group, 12 males and 17 females. Twenty-three were bilateral and 6 unilateral. The causes of death in the bilateral group were as follows: uremia, 8 cases; diabetes, 6 cases; and 1 each of pyemia, carcinoma of rectum, carcinoma of tongue, pernicious anemia, prostatic abscess, suppurative arthritis, cirrhosis of the liver, primary hypertension, and chronic glomerulonephritis. The duration of renal symptoms varied from two weeks to three and one-half months. The involvement of the kidneys was usually severe, but in only 9 cases was renal insufficiency the major cause of death, and 1 of these was complicated by chronic glomerulonephritis.

The blood pressures were recorded in 13 of the 29 cases. In 5 of the 13 cases the systolic pressure was 150 mm. Hg or higher, the lowest being 150/100 and the highest 180/90. Four of the 5 cases with hypertension had renal arteriolosclerosis. Therefore we need not believe that hypertension in acute pyelonephritis is due to the renal infection. Weiss and Parker found only 1 instance of hypertension in their patients with acute pyelonephritis.

2. *Chronic Hematogenous Pyelonephritis.*—Infections of more than four months' duration may be classified as chronic. In this discussion only the nonobstructive type is considered. The symptoms vary with the severity of the disease. Frequently there are acute exacerbations at irregular intervals during which the symptoms are more pronounced.

During exacerbatons there are commonly fever, leucocytosis, renal tenderness or pain, nausea, pyuria, etc. In the intervals between acute attacks and in chronic forms of low intensity there may be only a low-grade fever, a loss of appetite or fatigability. Pyuria is found only during exacerbatons.

The disease may persist for many years before death is brought about by uremia or infection.

In the literature "chronic pyelonephritis" is applied almost exclusively to contracted kidneys, but a marked shrinkage of the kidneys is not a necessary feature. When death results from an acute exacerbation of a chronic infection, the kidneys may be of increased size (Case 9, Table II).

TABLE II

## BILATERAL CHRONIC PYELONEPHRITIS WITHOUT URINARY OBSTRUCTION

AUTOPSY NO.	AGE (YR.)	SEX	DURATION	BLOOD UREA NITROGEN MG. %	BLOOD PRESSURE	WEIGHT OF HEART (GM.)	WEIGHT OF KIDNEYS (GM.)	HYALINE ARTERIOLES
1. 34-2178	8	F	6+ yr.	208	125/90	110	Very small	?
2. 25-301	20	M	2 yr.	236	100/55	307	R. 70 L. 60	?
3. 39-2543	25	M	13 yr. 10 mo.	200	152/94	425	R. 75 L. 43	Chronic glomerulonephritis
4. 37-2186	27	F	7 mo.	210	130/90	300	R. 100	?
5. 39-1371	30	F	20 mo.	N.P.N. 286	112/74 140/80	325	R. 74 L. 100	0
6. 36-1442	14	F	28 yr. 6 yr.	199	198/140	290	L. 100	3
7. 26-615	15	M	24 yr.	86.2	152/88	280	280	0
8. 25-161	16	F	3 yr.	48	?	250	R. 520 L. 100	0
9. 30-1016	16	F	1 yr.	?	160/82	260	610	0
10. 10-1753	18	F	26 yr.	68	140/90 3 yr. 110/80 2 days	290	R. 100	?
11. 10-3851	18	F	14 yr.	N.P.N. 80	115/65	190	R. 40 L. 40	0
12. 36-1278	19	F	10 mo.	52	195/100	295	R. 290 L. 150	Acute thromboarteritis
13. 28-1642	18	M	9 yr.	145	?	350	R. 60 L. 150	0
14. 19-224	50	M	2 yr. 8 mo.	P.S.P. 35	115/70	195	300	0

Both Staemmler and Pfeiffer found pyelonephritic contracted kidneys very common in autopsy material, and estimated that from one-fourth to one-third of contracted kidneys were of this type. From one-third to one-half of their cases were unilateral. But these estimates



must include types of disease which we have classified as hydronephrosis and unilateral dwarfed kidneys. In our 32,360 autopsies there are only 14 cases of chronic bilateral pyelonephritis of the nonobstructive type, and only 8 of these were typical bilateral contracted kidneys. The disease is more common in females than in males.

The macroscopic changes in the kidneys are characteristic and have been well described by Staemmler and Pfeiffer. The external surfaces show coarse sunken areas separated by islands of persistent cortex (Fig. 2, 1). The sunken areas are regions of marked cortical atrophy, and the elevated areas are portions of intact cortex. The extent of the atrophy of course may be greater in unilateral than in bilateral disease. The thin cortices of the kidneys give an impression of hydronephrosis, although there is little or no enlargement of the pelvis.

In the atrophic areas there is a dense lymphocytic infiltration especially marked in the medulla. The cortex corresponding with the infiltrated medulla may show some lymphocytic exudate but the principal change is atrophy. The first stage of the disease is a cortical inflammation with a spread of the cellular exudate from the cortex into the medullary pyramids. As a result of destruction of tubules the corresponding cortical segments undergo a slow disuse atrophy which results in the formation of large deep cortical depressions. The infiltrate usually has a patchy distribution leaving areas of normal parenchyma between the atrophic portions. The amount of persisting parenchyma in a pyelonephritic contracted kidney naturally depends upon the extent of the original inflammatory exudate.

In bilateral forms of pyelonephritis death occurs before atrophy has reached the extreme degree that is found in unilateral cases. The atrophic cortical areas are interspersed with normal tubules and glomeruli. The completely atrophied segments are composed almost entirely of hyaline glomeruli and atrophic tubules (Fig. 2, 2).

In unilateral disease the atrophy may become extreme, and in such instances the thin cortex may consist only of hyaline glomeruli, small tubules filled with casts, and atrophic arteries (Fig. 2, 3).

The arteries supplying the atrophic segments of the kidneys show thickened walls (Fig. 2, 3 and 4) and this appearance has been mistaken for primary arterial disease (Weiss and Parker). But this vascular change is a disuse atrophy, an adjustment of the lumen of the vessel to its decreased blood flow. Microscopic examination of medium-sized arteries shows that the intimal thickening is due to reduplication of the internal elastic lamella. One would expect this to be a collagenous intimal thickening, as in the Jores type, but it is elastic tissue. It is independent of hypertension since it occurs in chronic pyelonephritis with normal blood pressure.

In disuse atrophy the small renal arteries and arterioles show thick walls chiefly the result of contraction. The internal elastic lamella is not reduplicated but shows very marked folding corresponding with

the decreased size of the lumen (Fig. 3, 5). The most conspicuous alteration in these vessels is medial fibrosis, the smooth muscle being partly replaced by collagenous fibers. In chronic glomerulonephritis the afferent arterioles of hyaline glomeruli show small lumina and their walls have a semihyaline appearance (Fig. 3, 6). With the azocarmine stain it is seen that this homogeneous appearance is due to medial fibrosis (Fig. 3, 7). There is no intimal change. Occasionally in disuse atrophy the small arteries show collagenous intimal thickening.

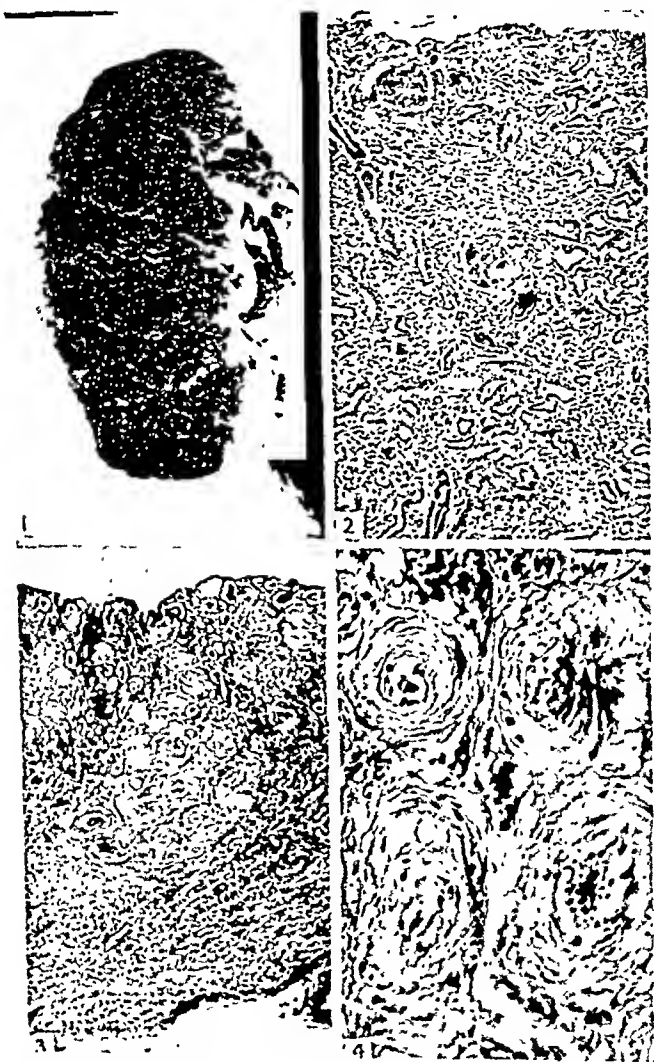


Fig. 2.—1. Case 11, Table II. Chronic hematogenous pyelonephritis. External surface of kidney. Photograph, natural size. 2. Case 11, Table II. Segment of atrophic cortex in chronic pyelonephritis. Note the severe tubular atrophy. 3. Unilateral hydronephrosis complicated by pyelonephritis. Note the extremely thin cortex, the inflammatory exudate near the pelvis epithelium, the hyaline glomeruli, the thick-walled arteries, and the small tubules filled by casts. 4. Disuse atrophy of small arteries. Higher magnification of an area from 2. The arteries show medial fibrosis.

Weiss and Parker described several cases of pyelonephritis with the vascular changes of malignant hypertension, but it is highly improbable that there is any causal connection between these two diseases.

#### BLOOD PRESSURE IN CHRONIC PYELONEPHRITIS

1. *Bilateral Pyelonephritis.*—Several writers have noted that bilateral pyelonephritis is occasionally accompanied by hypertension. Haslinger,

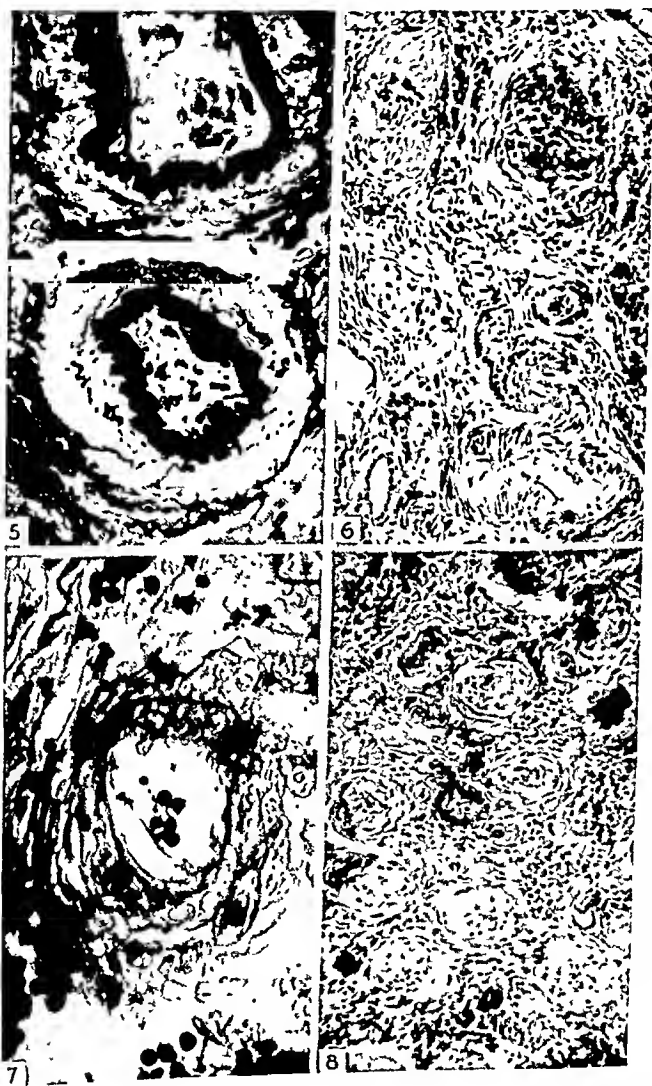


FIG 3.—5. Case 11, Table II. Ch arteries. Note the extreme folding of the lumen. Orcen stain. 6. Chronic atrophy of a hyaline glomerulus. 7. Disuse atrophy of an afferent arteriole of a hyaline glomerulus, showing medial fibrosis. Azocarmine stain. 8. Kidney of a dog. Severe atrophy of kidney due to constriction of renal artery. The blood pressure was high for eighteen months but then returned to normal and remained so for one year before the experiment was terminated. Note hyaline glomeruli and almost complete disappearance of tubules.

1928, found no noteworthy increase of blood pressure, but Staemmler as well as Pfeiffer found the pressure elevated not infrequently. Weiss and Parker found hypertension in about 50 per cent of their patients, but these investigators have confused their records by the inclusion of several obvious cases of malignant hypertension.

Longcope, who is often quoted on this topic, stated that the blood pressure is seldom elevated during the early stages of the disease, but that hypertension was present in 10 of 15 advanced cases. But of the 10 cases with hypertension 5 had renal arteriosclerosis and 1 had chronic glomerulonephritis.

Crabtree is not impressed with the frequency of hypertension in chronic pyelonephritis, since only 2 of 30 women with this disease under his observation had hypertension.

The blood pressure was recorded in 12 of our 14 cases of chronic bilateral pyelonephritis (Table II). Hypertension was present in 5 cases, but 1 of these (Case 3) also had chronic glomerulonephritis, and another had severe renal arteriosclerosis (Case 6). In Case 12 there was a terminal acute thromboarteritis which was presumably responsible for the hypertension. The size of the hearts, as shown in Table II, is evidence that none of these patients had a prolonged severe elevation of blood pressure such as occurs in primary hypertension; the only instance of cardiac hypertrophy was in the case of chronic glomerulonephritis (Case 3).

It may therefore be said that moderate hypertension occurs occasionally in uncomplicated chronic bilateral pyelonephritis, but a severe prolonged hypertension with cardiac hypertrophy in this disease is usually due to a complicating lesion such as chronic glomerulonephritis or renal arteriosclerosis.

An illustrative example of chronic bilateral pyelonephritis with contracted kidneys is as follows:

CASE 11 (Table II).—A married woman, 48 years of age, was first seen on March 26, 1940. She gave a history of an attack of "kidney trouble" fourteen years previously. Two years ago she had another attack characterized by heavy albuminuria. For the past six months she had complained of poor appetite and loss of weight. Her blood pressure on admission was 115/65 mm. Hg. There was heavy albuminuria and many pus cells were found in the urine. The two hour excretion of phenolsulphonephthalein was 7 per cent. Nonprotein nitrogen was 60 mg. per cent. There was a normochromic anemia with 2,700,000 erythrocytes and 10.6 Gm. of hemoglobin. The temperature was 99° F. On May 19, 1940, the nonprotein nitrogen was 80 mg. per cent. Death occurred May 28, 1940.

*Autopsy.*—There was no edema. The heart weighed 190 Gm. Fatty metamorphosis of the liver was present. Each kidney weighed 40 Gm. and showed granular surfaces and thin cortices. The pelvis and ureters appeared normal.

Microscopic study of the kidneys showed a heavy lymphocytic infiltration, especially marked in the medullary and deep cortical areas. There was widespread tubular atrophy and most of the glomeruli were hyaline (Fig. 2, 2). There were small islands of normal glomeruli and tubules. The arteries showed the changes characteristic of disuse atrophy. There was no hyaline arteriosclerosis.

A case illustrating a complication with chronic glomerulonephritis is as follows:

CASE 3 (Table II).—A male, 25 years old, known to have had albuminuria at the age of 12 years and nocturia for many years. He has had poor health for the past eighteen months and definite renal disease was recognized fourteen months before death. Upon admission, eleven days prior to his death, he was drowsy and had a uremic odor on his breath. The blood pressure was 157/88 and 152/94. Hemoglobin, 58 per cent; erythrocytes, 2,500,000; leucocytes, 10,800. Albumin, ++; specific gravity of urine, 1012. During a ten-day period with an average fluid intake of 2,320 c.c. the average amount of urine daily was 946 c.c. Blood urea nitrogen, 200 mg. per cent; creatinine, 21.7 mg. per cent.

At autopsy there was a slight dependent edema. The heart weighed 425 Gm. and showed left ventricular hypertrophy and moderate coronary atherosclerosis. The right kidney weighed 75 Gm. and the left 43 Gm. The pelves and right ureter were dilated, but the left ureter was of normal size. There was no obstruction in the urinary tract. The cortices of both kidneys were markedly atrophic and the external surfaces were covered with coarse depressions.

Microscopically the kidneys showed a heavy lymphocytic infiltration especially in the medullary portions. There were small scattered areas of persistent normal glomeruli and tubules but the great majority of the tubules were very atrophic and their glomeruli were hyaline. Many of the hyaline glomeruli showed evidence of an old proliferative glomerulonephritis, but the greater part of the atrophy was attributable to the heavy lymphocytic infiltration. The arteries and arterioles showed no changes except a moderate disuse atrophy.

The interpretation was that of a chronic pyelonephritis associated with chronic glomerulonephritis.

2. *Unilateral Pyelonephritis*.—In our autopsy records there are 94 cases of unilateral dwarfed kidney, but aside from 8 cases of true hypoplasia and 14 examples of unilateral polycystic disease it is usually impossible to determine the cause of the atrophy with certainty. In a few cases there was a lymphocytic exudate suggesting pyelonephritis, but in the vast majority there was no evidence of inflammation. With the exception of the cases of true hypoplasia and cystic disease the only change was atrophy, and the thick-walled arteries were evidence that the kidney originally had been much larger. In some instances it appeared that hydronephrosis was responsible for the atrophy and in other cases atherosclerosis of the large arteries was suggested.

None of the 94 cases was a "surgical" kidney in the sense that it was producing local symptoms. In the great majority the atrophy was so extreme that little or no functioning parenchyma remained.

Recently the chief interest in unilateral pyelonephritis has centered about its supposed relation to hypertension. Several cases have been reported in which a previously high blood pressure returned to normal after removal of the diseased kidney. At first it was only atrophic pyelonephritis that was supposed to cause hypertension, but now many urologists believe that any type of low-functioning or nonfunctioning

kidney may produce high blood pressure. Mulholland expressed the extreme view that all cases of hypertension should be studied urologically.

The theoretical argument for nephrectomy in hypertension with unilateral renal disease is based upon Goldblatt's experiments on dogs in which he showed that constriction of one renal artery usually causes moderate hypertension. The hypertension produced in this way is, however, not severe and does not persist permanently as it does when both renal arteries are constricted. It is believed that the ischemic kidney secretes renin which causes elevation of blood pressure. A very important feature of this experiment, frequently overlooked, is the fact that if the constriction of the artery is severe enough to produce atrophy of the kidney, the blood pressure will return to normal after the atrophy is well advanced. In the experiment which Pedersen and I performed, viz., obstruction of one renal vein, the blood pressure returned to normal after two months and it was found that the obstructed kidney was markedly atrophic. In 2 dogs with bilateral constriction of the renal arteries, which I have studied, the blood pressure was high for over eighteen months but then fell to normal levels and remained so for about one year before the animals were killed. At autopsy in each case one kidney had developed a collateral circulation and was normal while the other showed extreme atrophy. There is extensive lymphocytic infiltration and the only persistent parenchyma is represented by groups of small tubules filled with casts (Fig. 3, 8). These atrophic kidneys in the dogs were evidently incapable of producing renin, and it may therefore be argued that human atrophic kidneys with minimum amounts of parenchyma are likewise incapable of producing renin. There is no feature of the Goldblatt experiment which justifies the removal of a completely atrophic human kidney.

The literature concerning the effect of nephrectomy on hypertension is summarized in Table III. Twenty-five cases are recorded in which a small kidney with little or no function was removed in the hope that a fall of blood pressure would result. Cases 2, 13, 15, and 16 cannot be considered cured since the duration of the postoperative period of normal blood pressure was not given. Similarly Cases 5, 6, and 14 must be omitted from consideration since the period of observation was too short. It is well known that nonspecific operations such as hysterectomy often cause hypertension to subside for several months. The former practice of extracting teeth as treatment for hypertension was based upon the observation that a temporary fall of blood pressure frequently resulted.

In Case 18 the evidence of hypertension is hardly satisfactory and in Case 19 the marked variation in the preoperative blood pressure throws doubt upon the result. There are only 5 cases (Cases 3, 10, 21, 23, and 24) in which the blood pressure fell to normal and remained so for one year or longer.

In Crabtree's cases (Cases 11 and 12) the blood pressure showed a postoperative fall but subsequently returned to a high level. Three cases have come under my personal observation: 2 females, aged 14 and 26 years, and 1 male 9 years old. Each had severe hypertension of long duration and one low-functioning small kidney that was producing no renal symptoms. In the 2 females the small kidneys showed

TABLE III

EFFECT OF NEPHRECTOMY ON HYPERTENSION WITH UNILATERAL RENAL DISEASE

AUTHOR	DATE	AGE	SEX	PREOP- ERATIVE BLOOD PRES- SURE	POSTOP- ERATIVE BLOOD PRES- SURE	INTERVAL	LESION
1. Boyd and Lewis	(1938)	31	M	180/100 200/120	124/84	6.5 mo.	Large infarct
2. Leadbetter and Burkland	(1938)	5	M	170/110 145/85	Normal	?	Ectopic kidney; muscle plug in artery
3. Nesbit and Ratliff	(1940)	37	M	180/110	Normal	1 yr.	Pyelonephritis
4. Nesbit and Ratliff	(1940)	35	M	200/110	140/80	10.5 mo.	Small, contracted
5. Nesbit and Ratliff	(1940)	58	M	205/110	150/110	2 wk.	?
6. Nesbit and Ratliff	(1940)	47	F	190/120	120/95	13 days	Pyelonephritis, hy- dronephrosis
7. Nesbit and Ratliff	(1940)	28	F	220/110 280/140	220/110	3 mo.	Pyelonephritis, ar- teriosclerosis
8. Nesbit and Ratliff	(1940)	40	F	200/120	200/125	?	25 Gm., arterio- sclerotic
9. Nesbit and Ratliff	(1940)	24	M	170/100	130/64	5 mo.	Hydronephrosis
10. Barney and Suby	(1939)	10	F	185/130	98/60	21 mo.	Pyelonephritis
11. Crabtree	(1938)	14	M	250/170	130/? high	1 wk. 1 yr.	Hydronephrosis
12. Crabtree	(1938)	27	F	180/? 210/?	120/76 145/90 196/124	3 wk. 6 yr. 11 yr.	Pyelonephritis, glomerulone- phritis ?
13. Crabtree	(1938)	40	M	160/120 130/?	low	?	?
14. Ratliff	(1939)	51	F	180/100	120/80	At dis- charge	Tuberculosis
15. Ratliff	(1939)	32	M	230/170	155/110	?	Arteriosclerosis
16. Quinby	(1923)	14	M	250/170	138/90	?	Hydronephrosis
17. McIntyre	(1939)	34	M	180/104	134/78	10 mo.	Pyelonephritis
18. Bothe	(1939)	7	F	130/85	110/65	4.5 yr.	Pyelonephritis
19. Butler	(1937)	7	M	122/90 168/110	115/75	20 mo.	Pyelonephritis
20. Butler	(1937)	10	F	190/120	92/70	3 mo.	Pyelonephritis
21. Barker and Walters	(1940)	42	M	170/120 200/140	130/90	2 yr.	Pyelonephritis
22. Barker and Walters	(1940)	46	M	170/110	115/85	6 mo.	Pyelonephritis
23. Barker and Walters	(1940)	34	F	180/115	122/92	1 yr.	Pyelonephritis
24. Barker and Walters	(1940)	52	F	186/110	125/85	1 yr.	Pyelonephritis
25. Barker and Walters	(1940)	7	F	205/150	110/77	3 mo.	Pyelonephritis

chronic pyelonephritis and arteriosclerosis; in the male there were only arteriosclerosis and arteriolosclerosis. The kidneys contained only minimal amounts of functioning parenchyma. Nephrectomy had no favorable effect on the hypertension in these 3 cases; there was not even a temporary decrease.

In our 94 cases of unilateral dwarfed kidney there are 44 in which the blood pressure was recorded (Table IV). Twenty-eight of the 44

TABLE IV  
UNILATERAL DWARFED KIDNEYS

SERIAL NO.	AUTOPSY NO.	AGE	SEX	WEIGHT OF RIGHT KIDNEY	WEIGHT OF LEFT KIDNEY	WEIGHT OF HEART	BLOOD PRESSURE	DISEASE
1.	36-1625	55	M	213	45	355	140/68	True hypoplasia
2.	37-781	65	M	60	250	400	116/92	True hypoplasia
3.	39-742	55	F	225	75	325	120/70	True hypoplasia
4.	32-548	60	M	250	95	380	160/94	Polycystic
5.	35-1887	62	F	42	107	650	220/136	Polycystic
6.	37-901	79	M	170	45	500	125/86	Polycystic
7.	28-1191	42	F	20	190	400	196/90	
8.	28-1446	29	F	70	10	430	114/74	
							194/124	
9.	29-675	74	M	270	60	?	145/75	
10.	30-976	77	M	30	220	360	200/105	
11.	30-1941	70	M	200	30	510	132/90	
12.	32-401	78	M	Normal	30	310	162/78	
13.	32-1983	87	F	150	40	320	104/56	
11.	34-1118	33	F	200	30	250	156/82	
15.	34-1301	65	F	16	209	440	180/110	
16.	34-1808	60	M	20	180	530	208/130	
17.	36-1090	36	F	240	20	400	142/90	
18.	37-184	55	M	230	65	460	174/120	
19.	37-571	33	M	190	30	700	256/160	
20.	37-1507	68	F	18	233	440	190/110	
21.	37-1800	57	F	145	35	590	170/110	
22.	37-1956	77	F	35	145	452	140/90	
23.	37-2157	13	F	15	70	190	210/150	Hypoplasia
24.	38-1779	66	M	Very small	260	300	112/90	Pyelonephritis
25.	39-411	87	M	50	185	500	110/60	
26.	39-793	74	M	190	10	?	225/132	
27.	45-293	66	F	150	18	?	180/?	
28.	29-1485	81	M	160	50	460	200/120	
29.	31-1737	64	M	193	44	520	230/140	
30.	33-1302	56	M	40	210	500	158/90	
31.	34-334	72	M	50	170	530	162/90	Arteriolosclerosis in both kidneys
32.	41-992	58	F	106	50	312	150/82	
33.	32-837	82	M	50	116	280	98/60	
34.	35-1675	84	F	150	35	520	178/80	
35.	35-2090	84	M	32	127	486	160/90	
36.	35-2102	55	F	59	183	450	146/90	
37.	36-177	16	M	115	30	375	172/116	
38.	36-856	51	F	40	110	520	236/120	
39.	36-1948	88	M	50	125	260	135/80	
40.	37-1016	69	M	175	27	605	220/120	Uremia
41.	37-2067	49	F	200	20	600	160/140	Uremia
42.	37-467	46	F	128	28	337	142/90	
43.	37-1086	60	M	150	37	534	145/95	
44.	36-1106	69	M	187	39	608	170/112	



In Crabtree's cases (Cases 11 and 12) the blood pressure showed a postoperative fall but subsequently returned to a high level. Three cases have come under my personal observation: 2 females, aged 14 and 26 years, and 1 male 9 years old. Each had severe hypertension of long duration and one low-functioning small kidney that was producing no renal symptoms. In the 2 females the small kidneys showed

TABLE III

EFFECT OF NEPHRECTOMY ON HYPERTENSION WITH UNILATERAL RENAL DISEASE

AUTHOR	DATE	AGE	SEX	PREOP- ERATIVE BLOOD PRES- SURE	POSTOP- ERATIVE BLOOD PRES- SURE	INTERVAL	LESION
1. Boyd and Lewis	(1938)	31	M	180/100 200/120	124/84	6.5 mo.	Large infarct
2. Leadbetter and Burkland	(1938)	5	M	170/110 145/85	Normal	?	Ectopic kidney; muscle plug in artery
3. Nesbit and Ratliff	(1940)	37	M	180/110	Normal	1 yr.	Pyelonephritis
4. Nesbit and Ratliff	(1940)	35	M	200/110	140/80	10.5 mo.	Small, contracted
5. Nesbit and Ratliff	(1940)	58	M	205/110	150/110	2 wk.	?
6. Nesbit and Ratliff	(1940)	47	F	190/120	120/95	13 days	Pyelonephritis, hy- dronephrosis
7. Nesbit and Ratliff	(1940)	28	F	220/110 280/140	220/110	3 mo.	Pyelonephritis, ar- teriosclerosis
8. Nesbit and Ratliff	(1940)	40	F	200/120	200/125	?	25 Gm., arterio- sclerotic
9. Nesbit and Ratliff	(1940)	24	M	170/100	130/64	5 mo.	Hydronephrosis
10. Barney and Suby	(1939)	10	F	185/130	98/60	21 mo.	Pyelonephritis
11. Crabtree	(1938)	14	M	250/170	130/? high	1 wk. 1 yr.	Hydronephrosis
12. Crabtree	(1938)	27	F	180/? 210/?	120/76 145/90 196/124	3 wk. 6 yr. 11 yr.	Pyelonephritis, glomerulone- phritis
13. Crabtree	(1938)	40	M	160/120 130/?	low	?	?
14. Ratliff	(1939)	51	F	180/100	120/80	At dis- charge	Tuberculosis
15. Ratliff	(1939)	32	M	230/170	155/110	?	Arteriosclerosis
16. Quinby	(1923)	14	M	250/170	138/90	?	Hydronephrosis
17. McIntyre	(1939)	34	M	180/104	134/78	10 mo.	Pyelonephritis
18. Bothe	(1939)	7	F	130/85	110/65	4.5 yr.	Pyelonephritis
19. Butler	(1937)	7	M	122/90 168/110	115/75	20 mo.	Pyelonephritis
20. Butler	(1937)	10	F	190/120	92/70	3 mo.	Pyelonephritis
21. Barker and Walters	(1940)	42	M	170/120 200/140	130/90	2 yr.	Pyelonephritis
22. Barker and Walters	(1940)	46	M	170/110	115/85	6 mo.	Pyelonephritis
23. Barker and Walters	(1940)	34	F	180/115	122/92	1 yr.	Pyelonephritis
24. Barker and Walters	(1940)	52	F	186/110	125/85	1 yr.	Pyelonephritis
25. Barker and Walters	(1940)	7	F	205/150	110/77	3 mo.	Pyelonephritis

Infection of the kidneys is present at autopsy about twice as frequently (61 to 83 per cent) in those with low urinary tract obstruction as in those with ureteral obstruction above the bladder (23 to 46 per cent).

The incidence of chronic hypertension in hydronephrosis is not greater than in a control population of corresponding age, but we have two examples of severe chronic hypertension associated with congenital bilateral hydronephrosis of long standing.

Cortical abscesses are frequent in post-mortem material, but only 40 cases of typical acute nonobstructive pyelonephritis were found in over 32,000 autopsies.

There were only 14 examples of chronic bilateral nonobstructive pyelonephritis in our autopsies. The available evidence indicates that this disease seldom causes chronic hypertension.

Unilateral chronic atrophic pyelonephritis probably does not cause chronic hypertension, but reports have been published of 5 cases in which the blood pressure has remained normal for over one year after nephrectomy. There may be some other explanation for these successful cases since many failures have been observed.

In unilateral renal ischemia produced by Goldblatt's method the blood pressure returns to normal if the ischemic kidney becomes markedly atrophic.

The thick-walled arteries in atrophic pyelonephritis represent disuse atrophy and not primary vascular disease.

#### REFERENCES

- Barker, N. W., and Walters, W.: *Proc. Staff Meet., Mayo Clin.* 15: 475, 1940.  
 Barney, J. D., and Suby, H. I.: *New England J. Med.* 220: 774, 1939.  
 Bell, U. T., and Pedersen, A. H.: *Ann. Int. Med.* 4: 227, 1930.  
 Bothe, A. B.: *J. Urol.* 42: 969, 1939.  
 Lloyd, C. H., and Lewis, L. G.: *J. Urol.* 39: 627, 1938.  
 Brady, L.: *J. Urol.* 27: 295, 1932.  
 Butler, A. M.: *J. Clin. Investigation* 16: 889, 1937.  
 Cabot, H.: *Lancet* 211: 53, 1926.  
 Cabot, H., and Nesbit, R. M.: *Ann. Surg.* 92: 766, 1930.  
 Chown, B.: *Arch. Dis. Child.* 2: 97, 1927.  
 Crabtree, E. G.: *Tr. Am. A. Genito-Urin. Surgeons* 31: 299, 1938; *J. Urol.* 42: 982, 1939.  
 Culver, H., Herrold, R. D., and Phifer, F. M.: *J. A. M. A.* 70: 1444, 1918.  
 Eisendrath, D. N., and Kahn, J. V.: *J. A. M. A.* 66: 561, 1916.  
 Fahr, Th.: *Virchow's Arch. f. path. Anat.* 301: 110, 1938.  
 Freeman, G., and Hartley, G.: *J. A. M. A.* 111: 1159, 1938.  
 Gruber, C. M., and Rabinovitch, J.: *J. Urol.* 24: 233, 1930.  
 Haslinger, K.: *Ztschr. f. urol. Chir.* 24: 1, 1928.  
 Hellstrom, J.: *Acta chir. Scandinav.* 57: suppl. 6, 1924.  
 Leadbetter, W. F., and Burkland, C. L.: *J. Urol.* 39: 611, 1938.  
 Longcope, W. T.: *Ann. Int. Med.* 11: 149, 1937.  
 McIntyre, D. W.: *J. Urol.* 41: 900, 1939.  
 McLane, C. M.: *Am. J. Obsl. & Gynec.* 38: 117, 1939.  
 Mulholland, S. W.: *J. Urol.* 42: 957, 1939.  
 Nesbit, R. M.: *J. A. M. A.* 98: 709, 1932.  
 Nesbit, R. M., and Rathcliff, R. K.: *J. Urol.* 43: 427, 1940.  
 O'Connor, V. J.: *J. Urol.* 30: 1, 1933.

(63 per cent) had hypertension. Of the 35 persons over 50 years of age, 67 per cent had hypertension. This is definitely higher than in Wetherby's dispensary patients (Table V), and it suggests a causal connection between unilateral dwarfed kidney and hypertension. But it is highly probable that hypertension with its associated vascular disease is responsible for the dwarfed kidney; i.e., that the dwarfed kidney is an effect and not a cause of hypertension. The few cases in which material from the large kidney was available showed hyaline arteriolosclerosis.

Interesting data on the relation of unilateral renal disease to hypertension are furnished by Pearman, Thompson, and Allen. These investigators found the incidence of hypertension in 500 cases of each of the following diseases as follows: pyelonephritis, 9 per cent; nephrolithiasis, 7 per cent; duodenal ulcer, 4 per cent; adenomatous goiter without hyperthyroidism, 10 per cent; disease of the gall bladder, 7 per cent. In 2,000 cases of hypertension the incidence of gall bladder disease was 4.4 per cent; adenomatous goiter, 2.5 per cent; duodenal ulcer, 1.3 per cent; and arthritis, 6.3 per cent. These data suggest that pyelonephritis, like adenomatous goiter and arthritis, is merely associated with hypertension and is not a causative factor.

The few cases of hypertension that appear to have been permanently relieved by unilateral nephrectomy may have been cases of acute hypertension.

Hydronephrosis shows no convincing relationship to hypertension. The frequency of hypertension with hydronephrosis in persons over 50 years of age is shown in Table V. It will be noted that there is no significant difference from Wetherby's control in dispensary patients. Very few of Wetherby's cases had any symptoms of hypertension. However, we have 2 cases of bilateral congenital hydronephrosis of long duration in which hypertension was a prominent feature.

TABLE V

HYPERTENSION IN HYDRONEPHROSIS; A COMPARISON WITH WETHERBY'S DISPENSARY PATIENTS

HYPERTENSION (150 MM. HG OR HIGHER) IN PERSONS OVER 50 YEARS OLD

	% MALES	% FEMALES
Wetherby (1,558 cases)	38	57.5
Hydronephrosis (present series) (481 cases)	46	52.0

## SUMMARY

The obstructive form of pyelonephritis is about twelve times as frequent as the nonobstructive type in autopsy material. Its age and sex distribution corresponds with that of hydronephrosis, and the symptoms are usually overshadowed by those of the disease causing the hydronephrosis.

Infection of the kidneys is present at autopsy about twice as frequently (61 to 83 per cent) in those with low urinary tract obstruction as in those with ureteral obstruction above the bladder (23 to 46 per cent).

The incidence of chronic hypertension in hydronephrosis is not greater than in a control population of corresponding age, but we have two examples of severe chronic hypertension associated with congenital bilateral hydronephrosis of long standing.

Cortical abscesses are frequent in post-mortem material, but only 40 cases of typical acute nonobstructive pyelonephritis were found in over 32,000 autopsies.

There were only 14 examples of chronic bilateral nonobstructive pyelonephritis in our autopsies. The available evidence indicates that this disease seldom causes hypertension.

Unilateral chronic atrophic pyelonephritis probably does not cause chronic hypertension, but reports have been published of 5 cases in which the blood pressure has remained normal for over one year after nephrectomy. There may be some other explanation for these successful cases since many failures have been observed.

In unilateral renal ischemia produced by Goldblatt's method the blood pressure returns to normal if the ischemic kidney becomes markedly atrophic.

The thick-walled arteries in atrophic pyelonephritis represent disuse atrophy and not primary vascular disease.

#### REFERENCES

- Barker, N. W., and Walters, W.: *Proc. Staff Meet., Mayo Clin.* 15: 475, 1940.  
 Barney, J. D., and Sulby, H. L.: *New England J. Med.* 220: 774, 1939.  
 Bell, E. T., and Pedersen, A. H.: *Ann. Int. Med.* 4: 227, 1930.  
 Boile, A. E.: *J. Urol.* 42: 969, 1939.  
 Boyd, C. H., and Lewis, L. G.: *J. Urol.* 39: 627, 1938.  
 Brady, L.: *J. Urol.* 27: 295, 1932.  
 Butler, A. M.: *J. Clin. Investigation* 16: 889, 1937.  
 Cabot, H.: *Lancet* 211: 53, 1926.  
 Cabot, H., and Nesbit, R. M.: *Ann. Surg.* 92: 766, 1930.  
 Chown, B.: *Arch. Dis. Child.* 2: 97, 1927.  
 Crabtree, L. G.: *Tr. Am. A. Genito-Urin. Surgeons* 31: 299, 1934; *J. Urol.* 42: 982, 1939.  
 Culyer, H., Hertold, R. D., and Phifer, F. M.: *J. A. M. A.* 70: 1441, 1918.  
 Essendrach, D. N., and Kahn, J. V.: *J. A. M. A.* 66: 561, 1916.  
 Fahr, Th.: *Virchow's Arch. f. path. Anat.* 301: 140, 1938.  
 Freeman, G., and Harlley, G.: *J. A. M. A.* 111: 1159, 1938.  
 Gruber, C. M., and Rabinovitch, J.: *J. Urol.* 24: 233, 1930.  
 Hashinger, K.: *Ztschr. f. urol. Chir.* 24: 1, 1928.  
 Hellstrom, J.: *Acta chir. Scandinav.* 57: suppl. 6, 1924.  
 Leadbetter, W. F., and Burkland, C. E.: *J. Urol.* 39: 611, 1938.  
 Longcope, W. T.: *Ann. Int. Med.* 11: 149, 1937.  
 McIntyre, D. W.: *J. Urol.* 41: 900, 1939.  
 McLane, C. M.: *Am. J. Obsl. & Gynec.* 38: 117, 1939.  
 Mulholland, S. W.: *J. Urol.* 42: 957, 1939.  
 Nesbit, R. M.: *J. A. M. A.* 98: 709, 1932.  
 Nesbit, R. M., and Rathoff, E. K.: *J. Urol.* 43: 427, 1910.  
 O'Connor, V. J.: *J. Urol.* 30: 1, 1933.

- Patch, F. S., and Reid, R. G.: *Tr. Am. A. Genito-Urin. Surgeons* 25: 1, 1932.
- Pearman, R. D., Thompson, C. J., and Allen, E. V.: *Proc. Staff Meet., Mayo Clin.* 15: 467, 1940.
- Pfeiffer, A.: *Ztschr. f. urol. Chir.* 36: 53, 1932.
- Quinby, W. C.: *Boston M. & S. J.* 189: 485, 1923.
- Ratliff, R. K.: *University Hosp. Bull., Ann Arbor* 5: 42, 1939.
- Scott, W. W.: *J. Urol.* 21: 527, 1929.
- Staemmler, M.: *München. med. Wehnsehr.* 79: 2005, 1932.
- Staemmler, M., and Dopheide, W.: *Virchow's Arch. f. path. Anat.* 277: 713, 1930.
- Sweet, J. E., and Stewart, L. F.: *Surg., Gynec. & Obst.* 18: 460, 1914.
- Thiemich, M.: *Jahrb. f. Kinderh.* 72: 243, 1910.
- Thomson, J., and McDonald, S.: *Quart. J. Med.* 3: 251, 1909-1910.
- Vermooten, V.: *J. Urol.* 30: 181, 1933.
- Von Illyés, G.: *Ztschr. f. Urol.* 33: 158, 1939.
- Weiss, S., and Parker, F.: *Medicine* 18: 221, 1939.
- Wetherby, M.: *Ann. Int. Med.* 6: 754, 1932.
- Wharton, L. R., Gray, L. A., and Guild, H. G.: *J. A. M. A.* 109: 1597, 1937.
- Wieland, E.: *Correspondenz-Blatt f. Schweizer Aerzte* 48: 68, 1918.
- Young, H. H.: *Bull. Johns Hopkins Hosp.* 53: 1, 1933.

# OBSERVATIONS ON THE DISTRIBUTION AND TRANSPORT OF GAS IN THE GASTROINTESTINAL TRACT OF INFANTS AND YOUNG CHILDREN

JOHN R. PAINE, M.D., AND CURTIS B. NESSA, M.D., MINNEAPOLIS, MINN.

*(From the Departments of Surgery and Radiology of the Medical School,  
University of Minnesota)*

## INTRODUCTION

INFORMATION obtained from the study of roentgenograms of the abdomen has come to play such an important role in the diagnosis and treatment of intestinal obstruction that it is necessary for all clinicians to have a clear understanding of certain normal variations



Fig. 1. Roentgenogram of the abdomen of an 18-month-old child. Accumulations of gas are seen in the stomach, small bowel, and colon.

in the x-ray appearance of intestinal gas in children and infants. While it is generally recognized that adults exhibit normally no gas in the small bowel which can be seen on the x-ray film, experience teaches that this is not so in children. Furthermore, if the diagnosis of in-

testinal obstruction due to congenital lesions is to be promptly recognized in newborn infants information as to the speed with which gas appears in the gastrointestinal tract and is transported through it should be available.

A few observations on these questions have already been recorded. Snow and Cassasa studied 50 newborn infants and found that whereas 25 of these exhibited unusually large amounts of gas in the small and large intestine when lying in the recumbent position, it largely disappeared in 22 of the infants after lying in a semi-inclined position for twenty-four hours. In their experience gas was found only rarely in the small intestine of infants over 3 months of age.



Fig 2—Roentgenograms of the abdomen of a 10-year-old child. Some gas is seen in the ascending colon and a greater quantity in the descending colon. None can be seen in the small bowel.

Thiele made x-ray examinations of 4 infants immediately after birth to determine how soon gas entered the gastrointestinal tract. In 1 instance, seven minutes after birth no gas was seen in the stomach or intestine, but in the other 3 cases at seven, ten, and thirty-five minutes after birth respectively gas was found to be present in the stomach or stomach and bowel.

Soveri injected air into the stomachs of infants and observed on roentgenograms the rate of its passage through the gut. Approximately thirty minutes was required for the stomach to empty itself of

injected air. Within one to two hours the small bowel was usually empty also. If the intestinal canal was empty, gas passed through the colon in one to two hours, but usually a slower rate prevailed.

The observations which are reported here were made with two questions in mind. It was desired to determine if accumulations of gas visible on the x-ray film were consistently found in the small bowel of infants and children and if so at what age these shadows disappeared. The second question was how soon after birth gas could be detected in the gastrointestinal tract by x-ray examination and how quickly transport of this gas through the bowel into the sigmoid colon and rectum occurred.



A.

Fig. 24-C—Serial x-ray films of a normal newborn infant. A. Six minutes after birth gas can be seen in the stomach.

#### METHODS OF OBSERVATION

To determine the distribution of gas in the small bowel of infants and children 46 patients on the Pediatric Wards of the University of Minnesota Hospitals were chosen. These patients were selected cases.



testinal obstruction due to congenital lesions is to be promptly recognized in newborn infants information as to the speed with which gas appears in the gastrointestinal tract and is transported through it should be available.

A few observations on these questions have already been recorded. Snow and Cassasa studied 50 newborn infants and found that whereas 25 of these exhibited unusually large amounts of gas in the small and large intestine when lying in the recumbent position, it largely disappeared in 22 of the infants after lying in a semi-inclined position for twenty-four hours. In their experience gas was found only rarely in the small intestine of infants over 3 months of age.



Fig 2.—Roentgenograms of the abdomen of a 10-year-old child. Some gas is seen in the ascending colon and a greater quantity in the descending colon. None can be seen in the small bowel.

Thiele made x-ray examinations of 4 infants immediately after birth to determine how soon gas entered the gastrointestinal tract. In 1 instance, seven minutes after birth no gas was seen in the stomach or intestine, but in the other 3 cases at seven, ten, and thirty-five minutes after birth respectively gas was found to be present in the stomach or stomach and bowel.

Soveri injected air into the stomachs of infants and observed on roentgenograms the rate of its passage through the gut. Approximately thirty minutes was required for the stomach to empty itself of

## DISTRIBUTION OF GAS

In Table I are listed the various conditions present in the 46 patients in whom the distribution of gas in the gastrointestinal tract was studied.

TABLE I

DIAGNOSIS	NUMBER OF PATIENTS
Normal infant	28
Asthma	1
Diabetes mellitus	2
Eczema	2
Injury of right eye	1
Strabismus	2
Congenital cleft palate	3
Congenital cleft lip	1
Pes cavus	1
Spastic paralysis	1
Talipes equinovarus	2
Tuberculous cervical adenitis	1
Torticollis	1



Fig. 70. Five hours and ten minutes after birth, gas has passed through the whole gastrointestinal tract. A small quantity can be seen in the rectum.

fully to exclude any condition which might occasion the presence of inhibitive (paralytic) ileus or other conditions affecting the bowel. In most instances observations were made a day or so before discharge. All of the older children were ambulatory at the time of the examinations. Without any preparation roentgenograms of the abdomen were made in the supine position. These films were then studied to determine the location of the intestinal gas.



Fig 3B —Twenty-three minutes after birth the amount of gas in the gastrointestinal tract has increased. Accumulations in the jejunum as well as the stomach can be seen.

In order to determine the time of appearance and speed of transport of gas through the gastrointestinal tract of newborn infants a series of roentgenograms was made for each of 7 normal babies in the Pediatric Nursery of the University of Minnesota Hospitals. The birth of each of these infants was uncomplicated. An attempt was made to take the first film as soon after birth as possible. Additional films were made at chosen intervals of time. Except for changes in position made necessary by their care these infants were all kept in the supine position during the period of the observations.

## DISTRIBUTION OF GAS

In Table I are listed the various conditions present in the 46 patients in whom the distribution of gas in the gastrointestinal tract was studied.

TABLE I

DIAGNOSIS	NUMBER OF PATIENTS
Normal infant	28
Asthma	1
Diabetes mellitus	2
Eczema	2
Injury of right eye	1
Strabismus	2
Congenital cleft palate	3
Congenital cleft lip	1
Pes cavus	1
Spastic paralysis	1
Talipes equinovarus	2
Tuberculous cervical adenitis	1
Torticollis	1



FIG. 20. Five hours and ten minutes after birth gas has passed through the whole gastrointestinal tract. A small quantity can be seen in the rectum.

The distribution of the gas in the gastrointestinal tract as seen on roentgenograms is indicated in Table II.

TABLE II

DISTRIBUTION OF GAS IN THE GASTROINTESTINAL TRACT OF INFANTS AND CHILDREN

PATIENT	AGE OF PATIENT	DISTRIBUTION OF GAS	
		SMALL INTESTINE	COLON
1	Newborn	++	++
2	Newborn	++	++
3	Newborn	++	++
4	Newborn	++	++
5	Newborn	++	++
6	Newborn	++	++
7	Newborn	++	++
8	Newborn	++	++
9	Newborn	++	++
10	6 hr.	++	++
11	6 hr.	++	++
12	1 day	++	++
13	3 days	++	++
14	4 days	++	++
15	6 days	++	++
16	6 days	++	++
17	7 days	++	++
18	7 days	++	++
19	8 days	++	++
20	9 days	++	++
21	9 days	++	++
22	10 days	++	++
23	2 wk.	++	++
24	2 wk.	++	++
25	2 wk.	++	++
26	2 wk.	++	++
27	2 wk.	++	++
28	2 wk.	++	++
29	5 wk.	++	++
30	10 mo.	++	++
31	10 mo.	++	++
32	13 mo.	+	+++
33	17 mo.	++	++
34	18 mo.	+	+++
35	21 mo.	+	+++
36	2 yr.	+	+++
37	2 yr.	+	+++
38	3 yr.	+	+++
39	3 yr.	+	+++
40	6 yr.	0	++++
41	7 yr.	+	+++
42	7 yr.	+	+++
43	7 yr.	0	++++
44	8 yr.	0	++++
45	9 yr.	0	++++
46	10 yr.	0	++++

## DISCUSSION

These results indicate that in infants under 18 months of age the gas present in the gastrointestinal tract which can be demonstrated by x-ray examination is about equally distributed between the small and large bowel. Between the ages of 18 months and 6 to 7 years this distribution gradually changes so that more of the visible gas comes

TABLE III  
THE TIME OF APPEARANCE AND TRANSPORT OF GAS THROUGH THE GASTROINTESTINAL  
TRACT OF NEWBORN INFANTS AS DETERMINED BY SERIAL ROENTGENOGRAMS

CASE NO.	STOMACH	DUODENUM	JEJUNUM	ILEUM	CECUM	ASCENDING COLON	TRANSVERSE COLON	DESCENDING COLON	SIGMOID COLON	RECTUM
1	6 min.		1½ hr.	2½ hr.						4½ hr.
2	40 min.		50 min.	2½ hr.		1½ hr.			6 hr.	
3			15 min.	40 min.			2½ hr.			4 hr.
4		6 min.	30 min.	1 hr.			2 hr.	3 hr.	4 hr.	
5			15 min.		15 min.		1½ hr.	3 hr.	4 hr.	
6		8 min.	50 min.	2½ hr.		3½ hr.			1½ hr.	
7	6 min.		40 min.	2 hr.				4½ hr.		5 hr.

to be present in the colon. After 6 to 7 years of age practically all the visible gas is seen in the colon. These observations furnish no information to explain this change in gas distribution. The importance of these facts in the diagnosis and treatment of intestinal obstruction in infants and children is obvious, however, for in such patients the presence of visible gas in the small bowel cannot be assumed to be necessarily due to intestinal stasis as is the case with older children



Fig. 4A-C—Serial x-ray films of a normal newborn infant. A. Six minutes after birth, a small quantity of gas can be seen in the stomach

and adults. This is not to say that roentgenograms of the abdomen are not of any value in cases of obstruction in infants and young children, but rather that they must be interpreted with care and with due allowance for the facts here brought forth. In the presence of small bowel obstruction the amount of gas present in the small bowel will be larger than normal and the diameter of the gas-filled coils will be greater.

TIME OF APPEARANCE AND SPEED OF TRANSPORT OF GAS IN THE  
GASTROINTESTINAL TRACT OF NEWBORN INFANTS

In Table III are presented the results of observations made in the course of a series of roentgenograms of the abdomen of 7 newborn infants. The first film in each series was taken as soon as possible after birth. The time indicated is the interval after birth at which the x-ray film was made. The portion of the gastrointestinal tract indicated is the most distal portion of the bowel in which gas could be seen.



Fig. 4B. After two and one-half hours, gas has passed down into the ileum.

## DISCUSSION

The rapid appearance of gas in the stomach and upper gastrointestinal tract in newborn infants as shown in Table III gives further confirmation to the swallowed air theory of the origin of most intestinal gas. The important fact with respect to intestinal obstruction in the newborn, such as congenital atresia of the small bowel, is that within four to six hours after birth one should regularly find gas in the sig-



moid colon and rectum. If the presence of a congenital type of obstruction is suspected the diagnosis may be confirmed much earlier if this fact is remembered.



Fig. 4C.—After four and one-half hours, a large quantity of gas can be seen in the rectum. Other accumulations are scattered through the entire gastrointestinal tract.

In another respect the transport of gas to the rectum within six hours is important. This has to do with cases of imperforate anus and atresia of the rectum. Wangenstein and Rice in 1930 described a means by which the length of the atresic portion of the anus and rectum could be determined. The infant is held in the inverted position and the mercury bulb of a thermometer is pressed into the anal dimple or passed into the rectum up to the area of atresia. If a roentgenogram is then taken, the distance between the gas shadow proximal to the atresia and the radiopaque mercury bulb gives an accurate idea as to the length of the atresic gut. Consequently the magnitude of the operative procedure which will be necessary to correct the defect may be accurately judged. Every surgeon of experience will appreciate the importance of such information before a contemplated operation.

The validity of this maneuver depends of course on the correctness of the assumption that gas has progressed up to the point of obstruction at the time the x-ray film is made. The observations here reported indicate that this test cannot be depended upon until the infant is 6 or more hours old. Whether or not the presence of the obstruction and retained meconium will increase the time interval before gas arrives at the point of obstruction is not known.

#### SUMMARY

Roentgenograms of the abdomen were made on 46 children varying in age from a few minutes to 10 years. All these infants were thought to have normally functioning gastrointestinal tracts. The distribution of the intestinal gas with respect to the small bowel and colon was studied and the following information obtained:

1. Up to 18 months of age gas is distributed about equally between the small bowel and the colon.
2. Between 18 months and 6 years of age more and more intestinal gas is found in the colon and less in the small bowel.
3. After 7 years of age, as in adults, no gas in the small bowel is seen on the x-ray film.

Serial roentgenograms of the abdomen were made on 7 newborn infants. The first film in each case was made as soon after birth as possible and others at convenient intervals. On these films the interval after birth at which gas appeared in the gastrointestinal tract and the speed of its transit to the rectum were studied. In each case gas was observed to be already present in the stomach, duodenum, or jejunum by the time the first film could be taken which was within six to fifteen minutes after birth. Within four to six hours after birth gas was present in the sigmoid colon or rectum.

#### REFERENCES

1. Snow, W., and Cassasa, C. S. B.: Postural Treatment of Tympanites, *J. A. M. A.* 101: 1463, 1935.
2. Saveri, V.: Der Verlauf der Luft durch den Verdauungskanal des Säuglings, *Acta paediat. (supp. 3)* 23: 160, 1939.
3. Thiele, P.: Zur Radiologie des Säuglingsmagen, *Ztschr. f. Kinderh.* 50: 152, 1917.
4. Wangensteen, O. H., and Rice, C. O.: Imperforate Anus: A Method of Determining the Surgical Approach, *Ann. Surg.* 92: 77, 1930.

# CYSTIC DEGENERATION OF THE OVARIES\*

## AN EXPERIMENTAL STUDY

JOHN C. WEED, M.D., AND CONRAD G. COLLINS, M.D., NEW ORLEANS, LA.

(From the Departments of Gross Anatomy and Gynecology, Tulane University of Louisiana)

OVARIAN cysts have interested medical authors for many years, and since Rokitansky's description<sup>1</sup> of cystic disease, numerous reports of ovarian conditions have appeared. Cystic degeneration of the ovaries has been repeatedly described under such terms as chronic oophoritis, sclerocystic oophoritis, eirrhosis of the ovary, and hydrops ovarii folliculi. In spite of the multiplicity of reports, the etiology of this condition has never been accurately determined. Earlier reports<sup>1-4</sup> have indicated that chronic infection of the ovary produced cystic changes. A few authors<sup>5, 6</sup> have comparatively recently ventured support of this theory. The consensus today is opposed to this view. Another theory as to the etiology of this state supported by continental investigators<sup>7, 8</sup> has proposed that sympathetic dysfunction will result in multiple ovarian cysts. With the advent of hormonology, the current trend of thought is to explain cystic degeneration of the ovaries upon an endocrinologic basis, primarily pituitary in origin. Investigators<sup>9-13</sup> have been able to cause rapid follicular growth and atresia by the use of pituitary implants and extracts. However, these changes have not proved to be permanent.

Interest in this problem was stimulated when several cases of young women with large prolapsed multicystic ovaries were observed. It was noted that when this condition obtained, there was associated with it extensive congestion in the veins of the infundibulopelvic and broad ligaments. This suggested the possibility that the underlying cause of the ovarian change was the altered position and vascularity of the gland, rather than an extrinsic factor.

The anatomic relationship of the ovary has been adequately described, and the vascular supply has been exhaustively studied by Sampson.<sup>14</sup> However, the effects of circulatory impairment have not received a great deal of attention. Butcher,<sup>15</sup> with ligation experiments, showed that germ cells have little resistance and soon perish, whereas the germinal epithelium may survive later to replenish the germ cells when collaterals are fully developed. Neugebauer,<sup>16</sup> likewise, showed that extensive necrosis with loss of function followed ligation of ovarian vessels. The question as to whether hysterectomy will ultimately lead to cystic degeneration of the ovaries has been debated by many authors without any

\*Aided by a grant from the Anonymous Research Fund.

Received for publication, June 6, 1911.

substantial proof that such a result will occur. Recent authors<sup>17-19</sup> have agreed that hyperemia of the ovary resulting from congestion is a probable cause of cystic degeneration by causing increased follicular activity.

Since no experimental support to this contention has been offered, it was felt that prolapse of the ovaries of animals artificially produced would cause passive vascular congestion. The ovarian changes resulting from such a procedure would indicate what effect hyperemia produced upon the follicular apparatus.

#### EXPERIMENTAL PROCEDURE

To study the effect of circulatory impairment upon the ovary caused by prolapse of the organ, two groups of animals were used. Rabbits and dogs were selected because of the ease of procurement and management, although they lacked the cyclic changes found in the primates.



Fig. 1.—Normal rabbit ovary. The section shows normal ovarian stroma with healthy primordial and vesicular follicles.

*I. Rabbits.*—In order to study the effect of circulatory impairment on rabbit ovaries, ligation experiments were performed on several groups of animals, by ligating the ovarian vessels on the utero-ovarian anastomosis on both sides. All animals were segregated and sacrificed after twelve weeks. Sections of each ovary were compared to sections of ovaries of normal rabbits (Fig. 1). The results conformed with those reported by Butcher and Nengebauer.

In other groups of animals (one to four in a group) partial deprivation of the vascular supply of both ovaries as well as artificial prolapse

of the organ was produced. In all of these animals, changes in the follicular apparatus corresponded to those in which ligation alone was performed.

Finally artificial prolapse of the ovary without impairment of the circulation was secured by suturing the free (autimesenteric) border of the ovary to the lateral abdominal wall. Sutures were introduced through the tunica albuginea opposite the hilum, avoiding the hilar vessels. In such a way each ovary was displaced from the paravertebral gutter to a new position about one inch lateral and vertical to its normal bed. All animals were sacrificed after twelve weeks.

RESULTS.—In those rabbits whose ovarian vessels were ligated extensive necrosis occurred in the ovary, marked by fibrosis, loss of follicular structure, and fibrinous deposits on the tunica albuginea. In some animals, the degeneration was not marked, involving only the follicular apparatus, with pyknosis of the ovular and granulosa cell nuclei.



Fig. 2.—Prolapsed rabbit ovary. The section shows cystic follicles lined with degenerate granulosa cells. The primordial follicles are atretic, and there is an increased fibrosis of the stroma.

In those animals in which the utero-ovarian anastomosis was ligated, similar changes were noted. All ova were degenerate, and atresia of the large follicles in which ova could not be demonstrated showed pyknosis of granulosa cell nuclei. Few prevesicular follicles were noted, and all follicles in the vesicular stage were atretic.

Artificial prolapse of the ovary, without vascular ligation, resulted in a somewhat different pathologic picture. Healthy follicles, both primordial and prevesicular, were demonstrable in all sections, but many

of each group showed atretic changes. All vesicular follicles were atretic, and many of these were markedly dilated (Fig. 2). The ovum was usually absent in the large follicles and, when present, exhibited coagulation necrosis of the cytoplasm and nuclear fragmentation. Many large spaces were lined with theca interna, having lost the granulosa

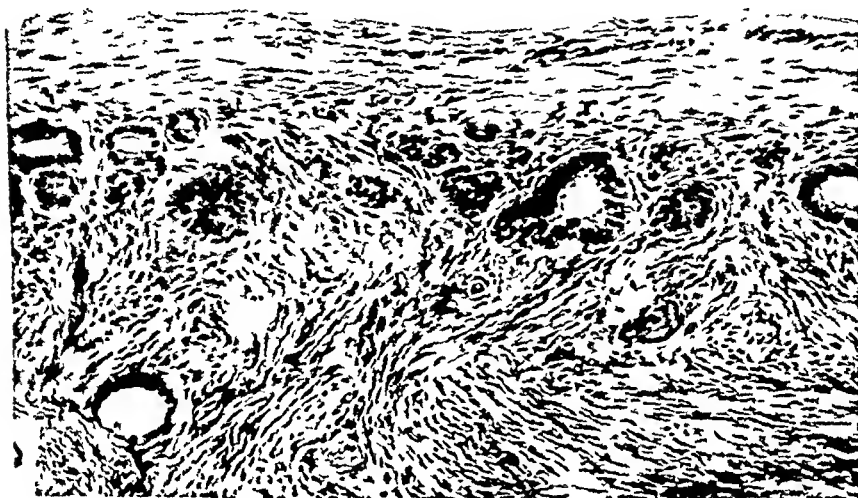


Fig. 3—Control dog ovary. A section through the cortex shows healthy primordial follicles and the normal thickness of the tunica albuginea

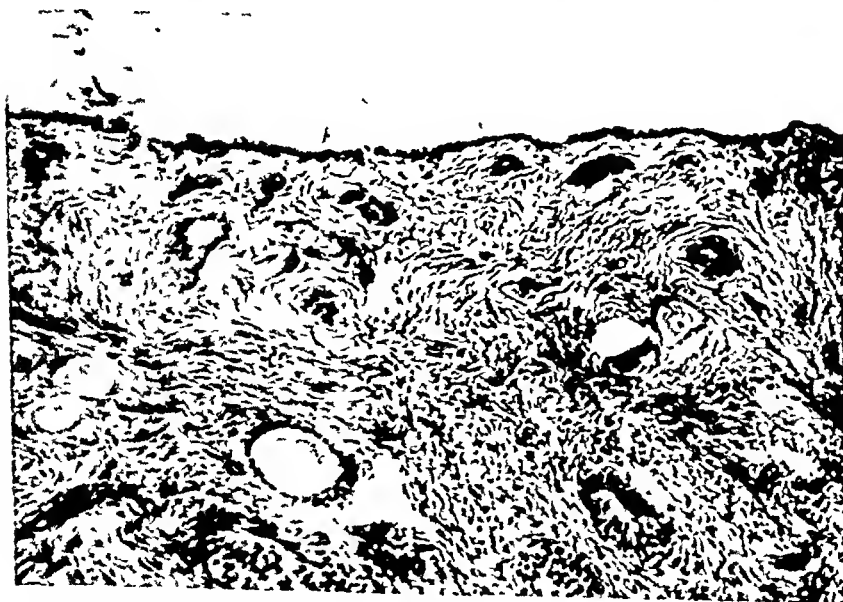


Fig. 4—Prolapsed dog ovary. This section under the same magnification as Fig. 3 shows the marked fibrosis of the tunica albuginea as a result of the prolapse. Many atretic primordial follicles can be seen

cell lining entirely. Aside from the extensive damage to the follicular apparatus, artificial prolapse produced vascular congestion in the medulla. Numerous dilated capillaries could be seen beneath the cortex. The tunica albuginea was thickened in many instances.

II. *Dogs*.—On a group of eleven dogs the left ovary was artificially prolapsed in a similar manner without vascular ligation. The right ovary was maintained in a normal position as a control. As in rabbits, the animals were castrated after twelve weeks, and sections of each ovary were studied.

RESULTS.—Examination of the dog ovaries did not show as striking changes as did those of the rabbit. The damage produced by artificial prolapse again centered around the follicular apparatus with congestion and fibrosis of the tunica albuginea secondarily. Again atresia was most evident in the larger vesicular follicles, although a greater number of atretic primordial follicles were noted in the prolapsed ovary. The large follicles were cystic, exhibiting no ovum, and degenerative changes were present in the granulosa cell layer when it was present. Capillary congestion was marked, and perifollicular edema was present. The tunica albuginea was thickened and fibrotic in almost all of the prolapsed ovaries (Figs. 3 and 4).

#### DISCUSSION

The changes produced in the experimental animals by artificial prolapse are chiefly vascular and affect the vesicular follicle primarily, producing follicular cysts. Small follicles are damaged to a lesser extent. Likewise an increased thickness of the tunica albuginea results from the altered position.

Such a picture is seen in the human ovary with cystic degeneration. Almost all follicles are large and atretic, with or without granulosa cells lining them. Smaller follicles are occasionally found, usually unaltered. Vascular congestion is prominent and thickening of the tunica albuginea is present, sometimes to a marked degree.

The presence of many follicular cysts in cases of cystic degeneration is evidence that normal maturation of the follicle does not occur in these individuals. Normal growth occurs to a point prior to maturity, but rupture of the follicle rarely occurs. Menstruation therefore is anovulatory in type. When cystic degeneration is fully developed, amenorrhea and menometrorrhagia develop, one following the other. Because of the menstrual disturbance and the anovulatory bleeding, sterility is a common complaint.

Treatment of cystic degeneration of the ovaries has varied from ignipuncture to removal. The former does not afford complete relief and the latter is too radical. Hormonal therapy, unfortunately, is not usually successful as many attest. Best results are obtained by partial resection of the ovaries with suspension.<sup>20-24</sup> Partial resection removes

the multicystic nonfunctioning area, as well as a large part of the thickened tunica albuginea. Suspension of the ovaries prevents the passive congestion with its secondary effects. Troublesome adhesion formation along the line of resection can be prevented by tying an omental graft along the suture line. It has been experimentally demonstrated that partial resection leaves a functioning ovary without undue destruction of the gland.<sup>25</sup> In 14 cases, restoration of function occurred in 10, partial success in 2, and failure in 2.

### CONCLUSIONS

1. Cystic degeneration of the ovaries, formerly thought to be the result of chronic infection, is now variously ascribed to sympathetic dysfunction and hormonal imbalance. Circulatory impairment is an infrequently considered but important etiologic factor.

2. Circulatory impairment was produced in the ovaries of eighteen rabbits by (1) vascular ligation and (2) artificial prolapse, and in one ovary of eleven dogs by artificial prolapse. Sections of these ovaries showed changes in the follicular apparatus analogous to those found in human ovaries with cystic degeneration.

3. The treatment giving the best results is partial resection and suspension of such cystic ovaries.

### REFERENCES

1. Tait, Lawson: *Diseases of Women*, New York, 1879, William Wood & Co.
2. Findley, P. P.: Cystic Degeneration of the Ovary, an Anatomical and Clinical Study of One Hundred and Eighty Cases, *Am. J. Obst.* 49: 762-771, 1904.
3. Humison, W. H.: Clinical and Microscopical Differentiation of Sclero cystic and Cirrhotic Degeneration of the Ovaries and Chronic Ovaritis, *J. A. M. A.* 35: 753-787, 1899.
4. Smend, L. F.: The Etiology and Pathology of Small Cystic Degeneration of the Ovary, *Ohio State M. J.* 8: 190-193, 1912.
5. Davis, C. H.: A Contribution to the Etiological Study of Ovaritis, *Surg., Gynec. & Obst.* 23: 560-567, 1916.
6. Condomin, R.: Essai de pathogénie de l'ovarite scléro-kystique; ses relations étiologique avec la douglassite, *Lyon méd.* 144: 681-691, 1929.
7. Castano, C. A., and Introzzi, A. S.: Nouveau procédé chirurgical pour le traitement de l'ovarite scléro-kystique, *Gynéc. et obst.* 22: 301-312, 1930.
8. DeCoulx, P., and Patoir, G.: Résultats de la chirurgie conservatrice pour l'ovarite scléro-kystique, *Bull. Soc. d'obst. et de gynéc.* 26: 82-85, 1937.
9. Fluhmann, C. F.: Comparative Studies of Gonad Stimulating Hormones: Effect of Prolonged Injections in Immature Rats, *Am. J. Physiol.* 106: 238-246, 1933; The Biologic Characteristics of Equine Gonadotropic Hormones, *West. J. Surg.* 48: 63-72, 1940.
10. Engle, E. T., and Smith, P. E.: Origin of the Corpus Luteum in the Rat as Indicated by Studies on the Luteinization of the Cystic Follicle, *Anat. Rec.* 45: 239, 1929.
11. Hamblen, E. C.: *Endocrine Gynecology*, Baltimore, 1939, Charles C Thomas, Publisher.
12. Smith, P. E.: Hastening Development of Female Genital System by Daily Homoplastic Pituitary Transplants, *Proc. Soc. Exper. Biol. & Med.* 24: 131-132, 1926.
13. Van Wageningen, G., and Morse, A. H.: Pregnancy Following Induced Cystic Changes in Ovaries, *Lancet* 1: 1220, 1938.



cell lining entirely. Aside from the extensive damage to the follicular apparatus, artificial prolapse produced vascular congestion in the medulla. Numerous dilated capillaries could be seen beneath the cortex. The tunica albuginea was thickened in many instances.

II. *Dogs*.—On a group of eleven dogs the left ovary was artificially prolapsed in a similar manner without vascular ligation. The right ovary was maintained in a normal position as a control. As in rabbits, the animals were castrated after twelve weeks, and sections of each ovary were studied.

RESULTS.—Examination of the dog ovaries did not show as striking changes as did those of the rabbit. The damage produced by artificial prolapse again centered around the follicular apparatus with congestion and fibrosis of the tunica albuginea secondarily. Again atresia was most evident in the larger vesicular follicles, although a greater number of atretic primordial follicles were noted in the prolapsed ovary. The large follicles were cystic, exhibiting no ovum, and degenerative changes were present in the granulosa cell layer when it was present. Capillary congestion was marked, and perifollicular edema was present. The tunica albuginea was thickened and fibrotic in almost all of the prolapsed ovaries (Figs. 3 and 4).

#### DISCUSSION

The changes produced in the experimental animals by artificial prolapse are chiefly vascular and affect the vesicular follicle primarily, producing follicular cysts. Small follicles are damaged to a lesser extent. Likewise an increased thickness of the tunica albuginea results from the altered position.

Such a picture is seen in the human ovary with cystic degeneration. Almost all follicles are large and atretic, with or without granulosa cells lining them. Smaller follicles are occasionally found, usually unaltered. Vascular congestion is prominent and thickening of the tunica albuginea is present, sometimes to a marked degree.

The presence of many follicular cysts in cases of cystic degeneration is evidence that normal maturation of the follicle does not occur in these individuals. Normal growth occurs to a point prior to maturity, but rupture of the follicle rarely occurs. Menstruation therefore is anovulatory in type. When cystic degeneration is fully developed, amenorrhea and menometrorrhagia develop, one following the other. Because of the menstrual disturbance and the anovulatory bleeding, sterility is a common complaint.

Treatment of cystic degeneration of the ovaries has varied from ignipuncture to removal. The former does not afford complete relief and the latter is too radical. Hormonal therapy, unfortunately, is not usually successful as many attest. Best results are obtained by partial resection of the ovaries with suspension.<sup>20-24</sup> Partial resection removes

# Recent Advances in Surgery

---

CONDUCTED BY ALFRED BLALOCK, M.D.

---

## THE SPHINCTER MECHANISM OF THE COMMON BILE DUCT IN HUMAN SUBJECTS

ITS REACTIONS TO CERTAIN TYPES OF STIMULATION\*

GEORGE S. BERGH, M.D., MINNEAPOLIS, MINN.

*(From the Department of Surgery, University of Minnesota Medical School)*

DURING the past few years new methods of investigation have led to great advances in the understanding of the activity of the human gall bladder and its relation to the discharge of bile into the duodenum. Until very recently, however, knowledge of the physiology of the sphincter of Oddi has been based largely upon the results of animal experimentation.

The discharge of bile into the duodenum is dependent upon the pressure of bile secretion, the activity of the gall bladder, and the tonus of the sphincter of the common duct. It is clear that deductions concerning sphincter activity cannot be made from observations of the amount of bile aspirated from the duodenum, since the relative importance of other factors regulating flow cannot be estimated under such conditions. Only direct measurements of sphincter tone are of value. Such measurements cannot be made in entirely normal individuals, but information can be secured from studies upon patients with intubation of the common bile duct. By investigations upon such subjects many significant observations have been made.

There are marked species differences between the sphincter of Oddi of man and that of the common laboratory animals, and, on the basis of structural differences, anatomists have anticipated that the activity of the human sphincter would differ in some respects from that of animals. While this review will contain references to experiments carried out upon animals, it will be concerned chiefly with the responses of the human sphincter to various types of stimulation and will include a report of the findings of a series of experiments which I carried out at the University of Minnesota.

\*This review includes material presented in a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Surgery, May, 1940. Protocols of individual experiments may be found in the original thesis.

14. Sampson, J. A.: Variations in the Blood Supply of the Ovary, and Their Possible Operative Importance, *Surg., Gynec. & Obst.* 24: 339-350, 1917.
15. Butcher, E. O.: Regeneration in Ligated Ovaries and Transplanted Ovarian Fragments of the White Rat (*Mus Norvegicus Albinus*), *Anat. Rec.* 54: 87-103, 1932.
16. Neugebauer, K.: Etude sur le développement de la circulation collatérale de l'ovaire de la lapine et son influence sur l'ovaire, *Compt. rend. Soc. de biol.* 123: 260-262, 1936.
17. Taylor, H. C.: Symptoms and Treatment of Follicle Cysts of the Ovary, *Am. J. Surg.* 33: 558-565, 1936.
18. Moench, C. L.: Etiology of Adenomyositis and Uterine Fibromyomata, *Am. J. Obst. & Gynec.* 18: 682-688, 1929.
19. Macomber, D.: Ovarian Deficiency as a Cause for Sterility, *Am. J. Obst. & Gynec.* 19: 739-747, 1930.
20. Reycraft, J. L.: Surgical Treatment of Ovarian Dysfunction, *Am. J. Obst. & Gynec.* 35: 505-512, 1938.
21. Lessnoi, S. K.: Die partielle Ovarialresektion bei Oligomenorrhöe und Amenorrhöe, *Arch. f. Gynäk.* 135: 250-255, 1928.
22. Scemla, J.: Ovarite sclero-kystique traitée par la resection partielle des ovaires: guérison des troubles menstruels et cessation d'une stérilité datant de huit ans, *Bull. Soc. gynéc. et d'obst.* 31: 782, 1936.
23. Stein, I. F., and Leventhal, M. L.: Amenorrhea Associated With Bilateral Polycystic Ovaries, *Am. J. Obst. & Gynec.* 29: 181-191, 1935.  
Stein, I. F., and Cohen, H. R.: Surgical Treatment of Bilateral Polycystic Ovaries, Amenorrhea and Sterility, *Am. J. Obst. & Gynec.* 38: 465, 1938.
24. Robinson, M. R.: Surgical Treatment of Ovarian Dysfunction; A Clinical and Pathological Study, *Am. J. Obst. & Gynec.* 30: 18-36, 1935.
25. Leltschuk, P.: Ueber die Partielle Resektion des Eiserstockes. Experimentell-histologische Untersuchung, *Arch. f. Gynäk.* 150: 545-582, 1932.

intestinal lumen. In this region it is accompanied by the principal pancreatic duct (Wirsung), and the two ducts usually unite (ampulla of Vater) just before emptying into the duodenum at the papilla major.\* This papilla is about 8 or 10 cm. from the pylorus and is located just above or just below a constant bend in the pars descendens of the duodenum which Schwegler and Boyden<sup>209-211</sup> have designated as the biliary flexure.

The intramural portion of the bile duct is considerably narrower than the extramural portion. Baggenstoss<sup>4</sup> attributes this to the distribution of the sphincteric and duodenal musculature, and also to the increased thickness of the mucous membrane in this region.

Schwegler and Boyden<sup>209-211</sup> have traced the development in the embryo, and have observed that, although the ampulla is at first co-extensive with the oblique intramural passage of the duct through the duodenum, it later recedes (beginning at the 20 mm. embryo stage) and near term it lies halfway between the tunica muscularis and the end of the papilla. Mann and Giordano,<sup>156</sup> in material obtained at autopsy, showed that in 76 per cent of their cases the ampulla of Vater was 2 mm. or less in length. In spite of this involution, the ampulla is an important structure because it gives rise to folds or valves which prevent the regurgitation of intestinal contents into the ducts.

As the bile duct and pancreatic duct enter the duodenal wall, they pass through a lengthwise hiatus in the longitudinal muscle and a transverse, eye-shaped fenestra in the circular muscle.† In the adult these slits have become narrow and have been filled partly by muscle bands that have grown in from the margins.

Boyden<sup>128</sup> has classified the muscles of the choledochoduodenal junction into (1) muscles of the choledochoduodenal aperture and (2) intrinsic muscles of the ducts and ampulla.

The former group includes the superior and inferior margins of the choledochal fenestra (which impinge on the ducts at only one level and differ in this respect from the anatomical arrangement in animals such as the dog), the reinforcing or R-fibers and the connecting or C-fibers. The R-fibers reinforce the angles of the fenestra, while the C-fibers connect the margins of the hiatus and fenestra with the papilla and the ducts.

The intrinsic muscles of the ducts and ampulla include: (1) the sphincter choledochus, (2) the longitudinal fascicles, (3) the sphincter pancreatens, and (4) the sphincter ampullae.

The sphincter choledochus is the most highly developed portion of the intrinsic sphincter of Oddi. It consists of an annular sheath of

\*The bile duct and pancreatic duct do not always have a common opening into the duodenum. Mann and Giordano<sup>156</sup> found separate openings in 31 per cent of 200 cases. Baggenstoss<sup>4</sup> collected reports describing 1,001 specimens, and in that group 43 per cent did not show an ampulla.

†The anatomical terms used in this description are those which have been accepted or introduced by Boyden and his associates.

## HISTORICAL SKETCH

Although attention has been devoted to the biliary tract since antiquity, an accurate knowledge of even the gross anatomic characteristics of this region was not acquired until the work of Vesalius (1543).<sup>223</sup> According to Boyden,<sup>36</sup> Vesalius recognized that some mechanism impeded the flow of bile from the choledochal orifice, but he did not identify an anatomic sphincter of the bile duct. The credit for first describing such a sphincter is extended to Glisson (1654),<sup>84</sup> who recognized "ring-like fibers" around the terminal portion of the duct.

Following Glisson, Bianchus (1711)<sup>27</sup> suggested the importance of contraction of this sphincter as a mechanism contributing to the filling of the gall bladder.

The American anatomist, Gage (1879), was the first to study the sphincter of the bile duct microscopically.<sup>80</sup> Oddi (1887), for whom the muscle has been named, carried out gross and microscopic investigations, and also was the first to study the function of the sphincter.<sup>170-180</sup> He noted the resistance to the flow of fluid which the sphincter mechanism exerted, and he observed the dilatation of the bile ducts which followed cholecystectomy in certain animals. He suggested that spastic contraction of the muscle might explain obscure clinical types of jaundice.

Morgagni (1761) had discussed the possible clinical significance of spasm of the bile duct more than a century before the time of Oddi,<sup>104</sup> but it is obvious from his writing that he had no clear understanding of the minute anatomical arrangement which might allow such a spasm to occur. He wrote concerning the rarer causes of jaundice: "I speak of spasmodic crampures, by which, at least, the orifice of the common duct, or the greater part of the small branches of the hepatic are constricted."

Although Oddi stated that he had extended his observations to include man, his descriptions were based upon his investigations in animals, and Znaniecki (1895) has been credited with being the first to describe the human sphincter histologically. The detailed study of Hendrickson (1898) appeared three years later.<sup>90</sup> Since that time a number of investigators, including Letulle and Nattan-Larrier,<sup>174</sup> Helly,<sup>98</sup> Job,<sup>118</sup> Mann,<sup>154</sup> Giordano and Mann,<sup>83</sup> Nuboer,<sup>173, 174</sup> Porsio,<sup>186</sup> Ivy,<sup>100-114</sup> and others have contributed further anatomical and physiologic data.

Present-day knowledge of the anatomy of the sphincter has been increased greatly by the contributions of Boyden and his associates,<sup>34-48, 209-211</sup> who have studied extensively its embryologic development as well as its structure in the adult.

## ANATOMICAL CONSIDERATIONS

The terminal portion of the common bile duct courses obliquely for a distance of 1 to 2 cm. through the duodenal wall before opening into the

intestinal lumen. In this region it is accompanied by the principal pancreatic duct (Wirsung), and the two ducts usually unite (ampulla of Vater) just before emptying into the duodenum at the papilla major.\* This papilla is about 8 or 10 cm. from the pylorus and is located just above or just below a constant bend in the pars descendens of the duodenum which Schwegler and Boyden<sup>209-211</sup> have designated as the biliary flexure.

The intramural portion of the bile duct is considerably narrower than the extramural portion. Baggenstoss<sup>4</sup> attributes this to the distribution of the sphincteric and duodenal musculature, and also to the increased thickness of the mucous membrane in this region.

Schwegler and Boyden<sup>209-211</sup> have traced the development in the embryo, and have observed that, although the ampulla is at first co-extensive with the oblique intramural passage of the duct through the duodenum, it later recedes (beginning at the 20 mm. embryo stage) and near term it lies halfway between the tunica muscularis and the end of the papilla. Mann and Giordano,<sup>156</sup> in material obtained at autopsy, showed that in 76 per cent of their cases the ampulla of Vater was 2 mm. or less in length. In spite of this involution, the ampulla is an important structure because it gives rise to folds or valvules which prevent the regurgitation of intestinal contents into the ducts.

As the bile duct and pancreatic duct enter the duodenal wall, they pass through a lengthwise hiatus in the longitudinal muscle and a transverse, eye-shaped fenestra in the circular muscle.† In the adult these slits have become narrow and have been filled partly by muscle bands that have grown in from the margins.

Boyden<sup>128</sup> has classified the muscles of the choledochoduodenal junction into (1) muscles of the choledochoduodenal aperture and (2) intrinsic muscles of the ducts and ampulla.

The former group includes the superior and inferior margins of the choledochal fenestra (which impinge on the ducts at only one level and differ in this respect from the anatomical arrangement in animals such as the dog), the reinforcing or R-fibers and the connecting or C-fibers. The R-fibers reinforce the angles of the fenestra, while the C-fibers connect the margins of the hiatus and fenestra with the papilla and the ducts.

The intrinsic muscles of the ducts and ampulla include: (1) the sphincter choledochus, (2) the longitudinal fascicles, (3) the sphincter pancreatens, and (4) the sphincter ampullae.

The sphincter choledochus is the most highly developed portion of the intrinsic sphincter of Oddi. It consists of an annular sheath of

\*The bile duct and pancreatic duct do not always have a common opening into the duodenum. Mann and Giordano<sup>156</sup> found separate openings in 31 per cent of 200 cases. Baggenstoss<sup>4</sup> collected reports describing 1,001 specimens, and in that group 43 per cent did not show an ampulla.

†The anatomical terms used in this description are those which have been accepted or introduced by Boyden and his associates.

muscle fibers surrounding the bile duct from a position just outside the window to the junction with the pancreatic duct. It is capable of obstructing the flow of bile without closing the pancreatic duct. In fact, Boyden<sup>41</sup> recently has described a case in which this muscle held a stone in the major papilla until it was too large to pass the orifice and was about to be discharged through a spontaneously developed fistula when the patient died.

The fasciculi longitudinales consist of two columns of longitudinal fibers lying between the choledochus and the pancreatic duct. They are made up of bands connecting different transverse levels of the ducts and ampulla and they are joined by the C-fibers. They probably serve to erect the papilla and thus facilitate the discharge of bile.

The sphincter pancreatus is an annular band of fibers around the lower end of the pancreatic duct. It is not constant.

The sphincter ampullae is an annular sheath of fibers surrounding the ampulla, when the latter structure is present, and also encircling the lower end of the bile and pancreatic ducts. Kreilkamp and Boyden<sup>128</sup> found it to be well developed in only one-sixth of adults. Contraction of this muscle prevents the flow of bile and pancreatic juice into the duodenum and may permit the reflux of bile into the pancreatic duct or of pancreatic juice into the bile duct.

#### PHYSIOLOGIC CONSIDERATIONS

Anatomists<sup>209-211</sup> have demonstrated beyond question the independent origin of a distinct sphincter at the terminal portion of the common bile duct, and Layne and I<sup>14</sup>,<sup>132</sup> have presented evidence to show that the sphincter of Oddi also functions independently of the duodenal musculature in man.

Giordano and Mann,<sup>83</sup> Lueth,<sup>138</sup> and Sandblom, Voegtlin, and Ivy<sup>200</sup> have observed an independent action of the sphincter in animals, but these same investigators, as well as others (Copher and Kodama,<sup>61</sup> Elman and McMaster,<sup>75</sup> Burget,<sup>52</sup> Brugsch and Horsters<sup>50</sup>), have demonstrated that, in animals, duodenal motility and tone exert a powerful influence on the flow of bile into the duodenum. To explain species differences in reactions, Boyden<sup>37</sup> has pointed out that there are marked species differences in the arrangement of the intestinal muscle around the bile ducts as well as in the intrinsic musculature. He states that: "In man, the window in the duodenal muscle through which the bile and pancreatic ducts enter the intestine is of such shape and size that duodenal peristalsis exerts a minimal effect on the flow of bile. By contrast the duodenal window of the dog has the shape of a funnel which envelops the first two-fifths of the intramural course of the bile duct."

On the other hand, McGowan, Knepper, Walters, and Snell<sup>140</sup> demonstrated, in a group of patients with postcholecystectomy colic, that spasm of the duodenum was associated with attacks of pain resembling

biliary colic, and that this pain could be relieved by intubation of the common bile duct. But the possibility remains that in their experiment both the pain and the simultaneous rise in the intraductal pressure may have been due to contraction of the sphincter within a spastic segment of the duodenum.

From the data presented by Layne and myself,<sup>14, 132</sup> one may conclude that, in man, the sphincter of Oddi does function independently. It is difficult to rule out entirely the factor of duodenal tone and motility in determining the resistance to the flow of bile, but anatomical observations indicate that it must be much less important in man than it is in animals. When we speak of the sphincter in a physiologic sense, however, we refer to the entire intramural regulatory mechanism, including both the action of the intrinsic sphincter and any influence which might be exerted by the muscle of the intestine.

The first activity to be attributed to the sphincter mechanism was the prevention of regurgitation of duodenal contents into the common bile duct (Glisson, 1654), and this is still regarded as one of its functions, although the mucosal folds or valves arising in the ampulla may be even more important in accomplishing this. When the sphincter action is eliminated, such as occurs in cases of internal biliary fistula, some degree of ascending infection follows.<sup>199</sup> This infection is usually slight and produces no clinical effect, but occasionally it may be severe. Wangenstein<sup>237</sup> has pointed out that an adequate stoma decreases the danger of cholangitis following anastomotic operations uniting the biliary tract and the gastrointestinal canal, but that narrowing or partial occlusion of the stoma favors infection. Recent experimental studies of Bachrach and Fogelson<sup>3</sup> substantiate Wangenstein's observation.

Gorham and Ivy<sup>87, 88</sup> have found that in some animals devoid of a competent sphincter there are other mechanisms for preventing regurgitation. There may be a one-way valve (as in the horse), large quantities of hepatic bile may keep the duets flushed out (as in the horse and pigeon), or the extrahepatic duets may show peristaltic activity (as in the pigeon).

A second function of the sphincter is to regulate the flow of bile into the intestine. The liver secretes bile continuously, but the latter is admitted to the duodenum only intermittently, depending upon the state of contraction of the gall bladder and of the sphincter of the bile duct. Whether or not the gall bladder evacuates when stimulated depends upon the resistance to flow of bile from the common duct into the duodenum. The maximum expulsive force of the gall bladder is 30 cm. of bile pressure,<sup>100</sup> while a spastic sphincter can resist a considerably greater force. If one grants that the gall bladder serves for the storage of bile for digestive purposes (and there is much evidence to support such a contention<sup>87, 88</sup>), this regulatory function of the sphincter is of considerable importance.



A third function of the sphincter is to aid in filling the gall bladder. If the sphincter mechanism be destroyed, the gall bladder does not fill and the bile flows directly into the intestine. Some physiologists believe that the chief function of the gall bladder is as a pressure regulatory mechanism to prevent the intraductal pressures from rising too high at times when the sphincter is closed. If such be the case, this third function of the sphincter is secondary to the function of preventing duodenal regurgitation, but if concentrated gall bladder bile has any advantage over unconcentrated hepatic bile in the processes of digestion, the part played in the filling of the gall bladder is an important function of the sphincter of Oddi.

A fourth function, attributed to the joint action of the longitudinal fascicles and the C-fibers, is to erect the papilla and facilitate the discharge of bile into the duodenum.

The extent of nervous control of the sphincter of Oddi is still not settled. The so-called Doyon-Meltzer law of reciprocal innervation of the gall bladder and sphincter of Oddi maintains that when the gall bladder contracts the sphincter relaxes as a result of reflex excitation, and during the storage of bile the sphincter is contracted and the gall bladder is relaxed. Evidence does indicate that there is a relationship between gall bladder and sphincter activity, but the mechanism of this relationship is not yet clear and the part played by the nervous system is not known. Some experimental evidence<sup>70, 106, 138, 240</sup> indicates that nervous regulation of the sphincter may be important in animals. Boyden,<sup>38</sup> however, suggests that nervous control of this muscle in man is probably less important than hormonal control. He has demonstrated that while experimentally induced spasm of the stomach will inhibit gall bladder evacuation in animals, this effect is not obtained in man. Furthermore, I<sup>9, 12</sup> have shown that the human sphincter of Oddi responds to a fatty meal even after the gall bladder has been removed, indicating that relaxation of the sphincter under such circumstances is not dependent upon a reciprocal relationship as postulated by the Doyon-Meltzer concept.

Recently Reich<sup>197</sup> has reported one human case in which he sectioned the descending nerve on the posterior aspect of the hepatic artery in an attempt to decrease sphincter tone. He reported that the procedure produced a decreased sphincter resistance and an altered response to the injection of morphine. Boyden<sup>40</sup> has pointed out that there are objections to accepting Reich's report as evidence of nervous control of the sphincter in man; and one of his students recently has demonstrated that elimination of the specific ("gastroduodenal") nerves to the choledochoduodenal junction markedly retards evacuation of the biliary tract (Johnson, 1941). Furthermore, subphrenic severance of the splanchnic roots of the celiac ganglia in these animals produces the

opposite effect, namely slight acceleration of flow, but it is believed that this is due to section of nerves inhibiting the gall bladder reflexes which are not present in man.<sup>45</sup>

Painful sensations identical with biliary colic may be produced by spastic contraction of the sphincter of Oddi in man. This was demonstrated first by Ivy, Voegtlin, and Greengard (1933), who produced such a spasm in a single case by the injection of a secretin-cholecystokin preparation,<sup>114</sup> and later by Butsch, McGowan, and Walters,<sup>55</sup> who observed colic in patients with sphincter spasm resulting from the administration of morphine. Zollinger<sup>246</sup> and Layne and Bergh<sup>13, 132</sup> have produced sphincter spasm associated with colic by sudden distention of the bile ducts. The pain in some cases remains localized in the epigastrium or right hypochondrium, while in other cases there is radiation to the interscapular or right subscapular region. Associated with the pain there is rigidity of the muscles of the abdominal wall, greatest in the right upper quadrant, and there may be inspiratory distress, and occasionally nausea and vomiting.<sup>9</sup>

Schrager and Ivy<sup>207</sup> have demonstrated that in animals similar pain responses may be abolished by splanchnic section, nausea and vomiting may be abolished by section of the vagi, and the respiratory disturbances are reduced by section of either the splanchnics or vagi. There is very little information concerning the sensory innervation of the sphincter area in man, but it has been assumed to be similar. Snell, McGowan, and Butsch<sup>215</sup> have reported three patients upon whom right splanchnic section was undertaken in an attempt to relieve postcholecystectomy pain. The results were satisfactory in one case and unsatisfactory in two. The failures were explained on the ground that the left splanchnic nerves, which had not been sectioned, may have carried sensory fibers. The more recent experiments of Boyden and Johnson<sup>47</sup> would indicate that persistence of pain might also be due to failure to interrupt the lesser splanchnic and first lumbar roots of the celiac plexus.

#### METHOD OF MEASURING SPHINCTER RESISTANCE

The sphincter resistance may be measured in patients with intubation of the common bile duct by a method similar in its essential principles to that employed in animal experiments by Mann,<sup>113</sup> Elman and McMaster,<sup>75</sup> and others.

My studies were carried out upon patients who previously had undergone cholecystectomy, choledochotomy, and intubation of the common bile duct. As a preliminary procedure the anatomical status of the bile ducts was demonstrated to be normal by cholangiographic examination. Several weeks were allowed to intervene between the operation and the time of the experiments, and the studies were carried out after the patients had fasted for eight hours. The investigations caused the

subjects no discomfort and anesthesia was not required. The patients rested quietly in bed in the supine position throughout all procedures.

The apparatus, which was sterilized in the autoclave, consisted of an infusion flask connected by a rubber tube to the choledochostomy tube. A Murphy drip bulb was included in the system so that observations of flow could be made. The perfusion fluid was sterile physiologic salt solution. At the beginning of each experiment all gas bubbles were evacuated from the system, except for a small air gap in the Murphy drip bulb.

By elevating or lowering the infusion flask, the pressure within the duct system could be altered, and it could be read directly on a centimeter scale which was adjusted so that the zero point was at the estimated level of the common bile duct. In such a system, when the ducts were filled with the perfusion fluid, there was no flow as long as the sphincter resistance was equal to, or greater than, the pressure exerted by the column of solution. When the perfusion pressure exceeded the sphincter resistance there was a flow which could be detected through the Murphy drip bulb. Since the distensibility of the bile ducts is relatively slight, any flow of fluid resulting from small changes of pressure could be assumed to indicate that the fluid was flowing into the intestine and that the sphincter resistance had been overcome.

The column of saline solution was adjusted to the exact level at which it was just supported without allowing any flow. At that point a drop of fluid would hang from the nozzle of the Murphy drip bulb where it would oscillate with respiration but would not fall. The pressure then was read directly on the scale and was recorded as sphincter resistance at that moment.

Measurements of sphincter resistance were made successively at frequent intervals and were recorded. After thirty to ninety minutes of preliminary measurements, various types of stimulation were applied in order to observe their effects upon the sphincter mechanism. Except when it was desired to investigate the combined action of drugs, only one type of stimulation was applied during a single day.

#### CRITICISM OF THE METHOD

At the outset it must be emphasized that this method measures the total resistance to flow of fluid from the bile duct into the duodenum, including any influence of the duodenal musculature as well as the activity of the sphincter proper. The fact remains, however, that the method does measure the resistance offered by the functional sphincter mechanism.

Factors such as friction in the tubes produce slight errors, but Mann<sup>153</sup> has demonstrated that these are insignificant and the values obtained are reasonably accurate.

The outstanding objection to the procedure is that the subjects upon whom the experiments were performed all had undergone cholecystectomy, and therefore, were not entirely normal.

Since the time of Oddi, a number of investigators have recognized that extirpation of the gall bladder in certain animals, such as the dog, cat, and goat,<sup>121, 176, 198</sup> and also in man,<sup>6, 120, 189-192</sup> may be followed by dilatation of the biliary ducts. In other animals, such as the guinea pig,<sup>204</sup> this postoperative dilatation does not occur. Several explanations have been advanced to account for this change.

The most widely accepted explanation is that the dilatation is the result of increased intraductal pressure following cholecystectomy. This theory depends upon a persistence of action of the sphincter of Oddi. In the absence of the gall bladder, which normally acts as a pressure regulator, the increased pressure must be accommodated by dilatation of the duct.

Considerable evidence favors the validity of this explanation. Judd and Mann<sup>121</sup> and Colp, Donbilet, and Gerber<sup>60</sup> were able to prevent dilatation of the ducts by eliminating the action of the sphincter. The latter investigators also found that section of the sphincter in four animals with dilatation of the bile passages following cholecystectomy resulted in a return of the ducts to normal diameter. Potter and Mann<sup>187</sup> observed an increased pressure within the common bile duct following cholecystectomy in dogs. Furthermore, dilatation of the ducts does not occur, or is only slight, following extirpation of the gall bladder in animals with very low sphincter resistance such as the guinea pig and rabbit.<sup>\*204</sup>

Pnestow,<sup>189, 192</sup> on the other hand, stated that there is permanent loss of function of the sphincter of Oddi following cholecystectomy. He first observed this in dogs with a special type of biliary fistula in which the exteriorized duodenum was slit open. From his experience with human subjects with choledochostomy tubes, he believes that there is a similar loss of sphincter tone following cholecystectomy in man.

Our observations, and those of other investigators upon human subjects, however, contradict this view. Walters and his associates, Donbilet and Colp, and Layne and Bergh have demonstrated that a resistance to the flow of fluid from the bile duct into the duodenum still exists in patients who have had extirpation of the gall bladder, and, in fact, actual spasm of the sphincter can be produced.<sup>11, 68, 142, 147, 226</sup>

\*Schmidt and Ivy<sup>2</sup> have studied many types of animals in regard to their output of hepatic bile, sphincter resistance, and physiologic capacity of the gall bladder, and have classified them into four groups. (Group I with a large bile output, low sphincter resistance, and absent gall bladder (jack rabbit, pigeon, horse, and rat). (Group II with a large bile output, low sphincter resistance, and gall bladder of low physiologic capacity (guinea pig, rabbit, and African bush rat). (Group III with a small bile output, moderately high sphincter resistance, and gall bladder of low physiologic capacity (sheep, goat, and cow). (Group IV with a small bile output, high sphincter resistance, and gall bladder of high physiologic capacity (man, dog, cat, duck, chicken, mouse, striped gopher). The fact that dilatation of the ducts following cholecystectomy occurs in animals listed in Groups III and IV but not in those listed in Group II favors the theory that the dilatation depends upon a persistent action of the sphincter pressure-regulating mechanism.

The more or less continuous flow of bile into the duodenum which has been observed in animals following cholecystectomy does not prove that the sphincter of Oddi has lost its tone. It indicates only that the sphincter resistance is smaller than the pressure under which the bile is being secreted. When the system has been filled with bile the pressure within the ducts must rise either until the sphincter resistance is exceeded, allowing flow into the duodenum, or until the secretory pressure is exceeded so that no more bile is formed. Variations in the sphincter resistance can make the flow of bile into the duodenum intermittent even in the absence of the gall bladder.

A second explanation of the dilatation of the ducts is based upon the assumption that there may be pressure transmitted into the common duct from the duodenum as a result of incompetence of the sphincter. This theory is based upon the observation that dilatation of the duct occurs following implantation of the common duct directly into the intestine<sup>83</sup> and also following cholecystoduodenostomy.<sup>190</sup> Under such conditions the action of the sphincter is eliminated. Bachrach and Fogelson,<sup>8</sup> however, suggest that in such cases the dilatation may be due rather to a temporary obstruction produced by swelling resulting from the operation.

Puestow<sup>191</sup> has offered a third theory, suggesting that the dilatation may be due to a loss of tonus of the wall of the bile ducts resulting from a local nervous derangement following cholecystectomy. Puestow, himself, recognized that the small amount of muscle in the wall of the ducts made such an explanation unlikely.

The evidence seems to indicate, therefore, that the ducts dilate because of persistence of activity of the sphincter mechanism. Whether the tone or response of the sphincter in man is altered by cholecystectomy cannot be stated definitely, since all studies have been made in individuals who have been operated upon. However, measurements of sphincter resistance in patients with choledochostomy tubes indicate that the sphincter does maintain tonus and activity following cholecystectomy, and the figures obtained are similar in range to those reported by many different investigators for the normal dog. In the absence of a method for studying the sphincter resistance in entirely normal human subjects, therefore, we are justified in accepting the results of experiments carried out according to the procedure which has been described.

#### NORMAL SPHINCTER RESISTANCE

Although the sphincter resistance cannot be determined in entirely normal individuals, we have considered the measurements obtained in individuals who had recovered from their operation, who were feeling well, and who had fasted for eight hours, as "normal." In such cases the sphincter usually withstood pressures between 9 and 23 cm. of

water. These figures are similar to those which Ivy and others quote as representing the normal intramural resistance in unanesthetized, fasting dogs. Our observations confirm the statement of Doubilet and Colp<sup>65</sup> that the average sphincter resistance in man is probably around 15 cm. of water.

Changes of a few millimeters in the intraductal pressure occurred during respiration, and marked changes were apparent during coughing, laughing, or vomiting, as a result of a temporarily increased intra-abdominal pressure. Even when the sphincter resistance appeared to be stabilized, changes of several centimeters' resistance occasionally occurred spontaneously without apparent cause. Often the initial measurements were slightly higher than those obtained subsequently.

#### IRRITABLE SPHINCTER

In some patients with choledocholithiasis, the sphincter remains irritable for several weeks, or even months, after the removal of a calculus from the common bile duct by operative procedure. In such cases the muscle readily goes into spasm and the intramural resistance may reach 30 or 40 cm. of water or more, and usually fluctuates through a wide range instead of becoming stabilized. We have supposed that such irritability is due to an inflammatory lesion (choledochitis secondary to stone). After several months of external drainage of the duct the irritability usually disappears and the sphincter apparently returns to "normal." McGowan and Henderson<sup>148</sup> also report that patients with an irritable sphincter have a lower "perfusion pain level" than patients with a more normal muscle.

These observations have led us to utilize sphincter resistance tests as one of the criteria for determining the proper time for removal of a choledochostomy tube.\*

As early as 1761, Morgagni<sup>164</sup> suspected that spasm of the bile duct might produce clinical disorders. Oddi, with his more complete understanding of the anatomical arrangement of the muscular sphincter of the duct, advanced this proposition. More recently the importance of sphincter spasm in its relation to symptoms has been emphasized by Schmieden and Niessen,<sup>200</sup> John Berg,<sup>6</sup> Meltzer,<sup>169</sup> Westphal, Gleichmann, and Mann,<sup>23, 240</sup> Ivy and Sandblom,<sup>113</sup> Walters,<sup>226</sup> Best and Hicken,<sup>1</sup> and others.

\*The criteria which we use to assist us in determining the proper time to remove a choledochostomy tube are: (1) cholangiographic evidence that the biliary tree is structurally normal, that no filling defects suggestive of stone are present, and that the contrast medium empties freely into the duodenum; (2) direct evidence that the sphincter resistance is normal and that the sphincter is not irritable; (3) subjective comfort of the patient, and lack of drainage around the tube when the catheter is clamped. If necessary, bile duct drainage may be continued for long periods of time without ill effect. One of our Wisconsin patients has carried such a tube for eight years coming to the clinic periodically for change of the catheter. In the case of prolonged drainage, it is necessary to change the choledochostomy tube at frequent intervals. Unless the external drainage of bile is complete or almost complete, it is not necessary to return the bile by mouth.

Presumably a purely functional derangement (biliary dyskinesia, biliary dyssynergia) may produce such spasm, but probably more the irritability of the sphincter is on an organic basis. Snell, McGee and Butsch<sup>215</sup> have suggested that local inflammatory processes induce sphincter spasm, and Ivy and Goldman<sup>110</sup> have pointed out inflammation of the ampulla could make the muscle hyperirritable. Reflex contractions of the sphincter secondary to disturbances in remote organs have not been demonstrated in man.

#### THE RESPONSE OF THE SPHINCTER TO FOOD

Many investigators have observed that the ingestion of food is followed by a flow of bile into the intestine. However, one may not infer from such an observation that food causes the sphincter to relax, for it is well known that certain food substances may cause both an increased secretion of bile and contraction of the gall bladder.

Winkelstein and Aschmer,<sup>244</sup> Cole,<sup>58</sup> McMaster and Elman,<sup>75, 150</sup> and others have reported that food influences the sphincter to relax in dogs. In human subjects there is little information concerning the question. Carter<sup>56</sup> has stated that the external drainage of bile from a choledochostomy tube is decreased after a meal, indicating relaxation of the sphincter. Walters<sup>227</sup> described one patient in whom biliary colic produced by morphine, was relieved partially after eating. Best and Hicken<sup>24</sup> inferred from cholangiographic evidence that cream and olive oil produced relaxation of the muscle. Using direct measurement of sphincter resistance, Doubilet and Colp<sup>68</sup> found that, in one case, a full meal did not influence the sphincter; in another patient a meal of soup, two eggs, and ice cream had no effect; and, in a third case, clear chicken soup produced slight relaxation.

Since information concerning the response of the human sphincter to food is fragmentary, I have<sup>12</sup> carried out a series of 34 experiments in an attempt to discover the effects of a fatty meal, a protein meal, and a carbohydrate meal.

Before undertaking these studies, it was established that the ingestion of water alone did not influence the sphincter tone. The effects of the different types of meals then were tested.

A fatty meal consisting of two raw egg yolks mixed in a glass of cream and flavored with sugar was given to 15 patients. In 4 additional cases a meal of 30 to 60 c.c. of olive oil was given. The oil was given by mouth in 2 cases and by duodenal tube in the others.

The protein meal, which was given to 4 patients, consisted of the whites of two eggs and two slices of lean, trimmed beef.

The carbohydrate meal, which was given to 8 patients, consisted of 20 c.c. of sweetened fruit juice and two thin slices of unbuttered white bread with fruit jam. In 3 other cases the effect of intravenous glucose

ministration of 250 to 500 c.c. of 10 per cent glucose solution was studied.

The egg yolk meal produced sphincter relaxation in 14 of the 15 experiments. The relaxation began following an average delay of four minutes after ingestion of the meal. Previous to the relaxation in one-half of the cases there was a brief initial increase in sphincter resistance. This initial elevation of sphincter tone might account for the frequently occurring "two-minute pause" preceding the initial phase of gall bladder emptying as described by Boyden.<sup>23</sup> The average maximum fall of sphincter resistance was 7 cm. of water pressure and occurred twenty-one minutes after ingestion of the food (average). The total average duration of the first phase of relaxation was thirty-four minutes. Subsequent fluctuations of sphincter resistance included relaxations and contractions of the muscle capable of determining later phases of gall bladder emptying. Periods of relaxation sometimes were observed for as long as two or three hours after the meal.

In the experiments in which olive oil was administered the effect was insignificant. The negative result might be due to the fact that fresh olive oil was used. Rost<sup>198</sup> has reported that old olive oil produces a flow of bile in dogs, but that fresh oil is ineffective. Best and Hicken<sup>22</sup> state that warm olive oil produces relaxation of a spastic sphincter, and that it is effective on the choledochal side as well as when it is placed into the duodenum.

The protein meal produced sphincter relaxation only once in 4 experiments. In the other 3 cases there was no effect. In dogs, Jacobson and Gydeson<sup>116</sup> observed some relaxation from protein stimulation, but McWhorter<sup>121</sup> found no effect.

Neither a carbohydrate meal nor 10 per cent glucose solution administered intravenously had any significant effect upon the sphincter.

These observations may be correlated with the well-known facts concerning the effects of food upon the gall bladder. Fats produce the greatest contraction of that organ, proteins rank next, and carbohydrates are practically ineffective in causing gall bladder evacuation.

Since the subjects upon whom the experiments were performed had undergone cholecystectomy, it is apparent that the responses of the sphincter of Oddi to food are not dependent upon the presence of the gall bladder. Contraction of the gall bladder and relaxation of the sphincter following a fatty meal appear to be independent reactions to the same stimulus.

#### THE EFFECT OF SODIUM BICARBONATE

It is well known that bile and bile salts stimulate an increased secretion of bile both in experimental animals and in man.<sup>170, 202, 248</sup> The use of these substances as therapeutic agents makes it desirable to learn their effect upon the constituent parts of the biliary system. It has been reported that they produce relaxation of the gall bladder<sup>100</sup> in addition



to their choloretic action. According to Winkelstein and Aschner,<sup>24</sup> bile salts produce a decrease of sphincter tone in dogs.

In 8 human subjects we studied the effect of the intravenous injection of 5 to 10 c.c. of 20 per cent sodium dehydrocholate. The results were variable. Slight relaxation of the sphincter occurred in 4 cases, there was no effect in 3 cases, and in 1 case an increased tone of the sphincter was produced. Best and Hicken<sup>20, 21</sup> reported an increased intraductal pressure after administration of sodium dehydrocholate to human subjects with choledochostomy tubes.

#### THE RESPONSE OF THE SPHINCTER TO DRUGS

In a series of 176 experiments, the effects upon the sphincter resistance following the administration of various drugs were studied. In the case of some of the drugs no comparable observations have been reported previously. In other cases the observations of earlier investigators were confirmed or contradicted. The obvious clinical value of knowing the action of various drugs upon the sphincter of Oddi requires no comment. Beyond that, however, certain inferences concerning the physiology of the sphincter may be drawn from the data which have been secured.

*Morphine.*—In 8 experiments we observed that morphine sulfate, in doses of  $\frac{1}{12}$  to  $\frac{1}{6}$  gr. subcutaneously, produced a prompt and prolonged increase in sphincter tone. (The increase in sphincter tone following the administration of any of the opiates which are included in this review may persist for more than two hours.)

Reach,<sup>103-105</sup> working with guinea pigs and rabbits, was the first to demonstrate that morphine produced a contraction of the sphincter of Oddi (1913). This was confirmed in dogs by Iwanaga,<sup>115</sup> Kitakoji,<sup>126</sup> and Lueth.<sup>138</sup> Butsch, McGowan, and Walters<sup>55</sup> showed that the same effect occurred in man, and our experiments, as well as those of Doubilet and Colp,<sup>68</sup> confirm this observation. Butsch, McGowan, and Walters reported that the effect of morphine was evident within two and one-half to five minutes after injection of the drug, and reached its maximum within fifteen minutes. Confirmatory results have been obtained by others.

J. Berg,<sup>8</sup> Butsch, McGowan, and Walters,<sup>55</sup> and Nygaard<sup>177</sup> have reported patients in whom morphine precipitated attacks of biliary colic. We have observed similar cases. Sometimes the sphincter spasm and the pain in such instances may be relieved by the administration of amyl nitrite<sup>55, 178</sup> or by a fatty meal.<sup>11</sup>

*Codeine (Methyl Morphine).*—Butsch, McGowan, and Walters<sup>55</sup> have reported that codeine produces a prolonged contraction of the sphincter, but that the elevation of sphincter tone is not as great nor as swiftly produced as in the case of morphine. In 6 experiments, using a 1 gr

dose of codeine administered subcutaneously, our results confirmed the observations of Butsch, McGowan, and Walters.

*Pantopon (Pantopium Hydrochloride).*—Pantopon consists of the isolated alkaloids of opium in their natural proportions. In 5 experiments we observed an effect from pantopon almost exactly like the effect produced by morphine. A prompt contraction of the sphincter followed the injection of  $\frac{1}{2}$  gr. doses of the drug, and the increased intramural resistance persisted for long periods of time.

Reach<sup>193</sup> was the first to show the action of this drug upon the sphincter (1920). He observed that it caused increased sphincter resistance in the guinea pig. Butsch, McGowan, and Walters<sup>55</sup> demonstrated a similar effect in man. Nygaard<sup>175</sup> reported having observed a patient with postcholecystectomy pain in whom pantopon induced attacks of biliary colic.

*Dilaudid (Dihydromorphinone Hydrochloride).*—Dilaudid is said to exert less effect upon the alimentary canal than morphine, but we found the effect of the two drugs upon the sphincter to be almost identical. In 4 experiments the subcutaneous injection of dilaudid (in doses of  $\frac{1}{32}$  gr.) was followed by a prompt contraction of the sphincter, with a prolonged elevation of the intramural resistance. Butsch, McGowan, and Walters<sup>55</sup> have reported similar findings.

*Amyl Nitrite.*—The nitrites and the organic nitrates which are reduced to nitrites in the body decrease the tone of smooth muscle generally, and as a result of that property have proved beneficial in certain cases of biliary colic.

In 1915, Lieb and McWhorter<sup>136</sup> demonstrated that amyl nitrite produced a loss of tonus in the isolated gall bladder of the dog. Reach,<sup>193</sup> however, was unable to show any significant effect upon the sphincter in guinea pigs.

Butsch, McGowan, and Walters<sup>55, 147, 213</sup> in their studies on human subjects found that inhalation of amyl nitrite immediately lowered an elevated intrabiliary pressure, whether the elevated pressure was spontaneous or the result of a previous injection of morphine. If pain was associated with the elevated pressure, it was relieved by the drug. Relief from biliary colic after inhalation of amyl nitrite has been reported subsequently by others.<sup>175, 225</sup>

Our experiments (11 cases) confirmed the observation that amyl nitrite produced relaxation of the sphincter. In most cases the relaxation was almost immediate, and the sphincter resistance returned to the original level within ten minutes. Occasionally, however, in the presence of a spastic sphincter, relaxation did not occur. In such instances the pain associated with the sphincter spasm did not disappear. Clinical experience supplements this observation, for many cases of biliary colic cannot be relieved by amyl nitrite.

to their choleric action. According to Winkelstein and Aschner,<sup>24</sup> bile salts produce a decrease of sphincter tone in dogs.

In 8 human subjects we studied the effect of the intravenous injection of 5 to 10 c.c. of 20 per cent sodium dehydrocholate. The results were variable. Slight relaxation of the sphincter occurred in 4 cases, there was no effect in 3 cases, and in 1 case an increased tone of the sphincter was produced. Best and Hicken<sup>20, 24</sup> reported an increased intraductal pressure after administration of sodium dehydrocholate to human subjects with choledochostomy tubes.

#### THE RESPONSE OF THE SPHINCTER TO DRUGS

In a series of 176 experiments, the effects upon the sphincter resistance following the administration of various drugs were studied. In the case of some of the drugs no comparable observations have been reported previously. In other cases the observations of earlier investigators were confirmed or contradicted. The obvious clinical value of knowing the action of various drugs upon the sphincter of Oddi requires no comment. Beyond that, however, certain inferences concerning the physiology of the sphincter may be drawn from the data which have been secured.

*Morphine.*—In 8 experiments we observed that morphine sulfate, in doses of  $\frac{1}{12}$  to  $\frac{1}{6}$  gr. subcutaneously, produced a prompt and prolonged increase in sphincter tone. (The increase in sphincter tone following the administration of any of the opiates which are included in this review may persist for more than two hours.)

Reach,<sup>193-195</sup> working with guinea pigs and rabbits, was the first to demonstrate that morphine produced a contraction of the sphincter of Oddi (1913). This was confirmed in dogs by Iwanaga,<sup>115</sup> Kitakoji,<sup>126</sup> and Lueth.<sup>138</sup> Butsch, McGowan, and Walters<sup>55</sup> showed that the same effect occurred in man, and our experiments, as well as those of Doubilet and Colp,<sup>68</sup> confirm this observation. Butsch, McGowan, and Walters reported that the effect of morphine was evident within two and one-half to five minutes after injection of the drug, and reached its maximum within fifteen minutes. Confirmatory results have been obtained by others.

J. Berg,<sup>8</sup> Butsch, McGowan, and Walters,<sup>55</sup> and Nygaard<sup>175</sup> have reported patients in whom morphine precipitated attacks of biliary colic. We have observed similar cases. Sometimes the sphincter spasm and the pain in such instances may be relieved by the administration of amyl nitrite<sup>55, 175</sup> or by a fatty meal.<sup>11</sup>

*Codeine (Methyl Morphine).*—Butsch, McGowan, and Walters<sup>55</sup> have reported that codeine produces a prolonged contraction of the sphincter, but that the elevation of sphincter tone is not as great nor as swiftly produced as in the case of morphine. In 6 experiments, using a 1 gr.

bile in most cases. The flow of bile into the duodenum, however, cannot be accepted as an indication of sphincter relaxation.

*Magnesium Sulfate.*—The use of magnesium sulfate for "nonsurgical biliary drainage" makes the study of its action upon the sphincter of Oddi of especial interest.

In 1917, Meltzer<sup>160</sup> suggested that if magnesium sulfate were introduced into the duodenum it might cause relaxation of the sphincter, and probably also contraction of the gall bladder ("Law of Contrary Innervation"). Lyon<sup>140, 141</sup> applied this suggestion to human patients and observed that the introduction of this drug into the duodenum induced a flow of bile which was light yellow at first (A bile), but which later became darker and more viscid (B bile).

McWhorter,<sup>151</sup> Jacobson and Gydeson,<sup>116</sup> Winkelstein and Aeshner,<sup>244</sup> Iwanaga,<sup>115</sup> Shi,<sup>213</sup> and others reported that it caused relaxation of the sphincter in dogs. Lueth<sup>138</sup> stated that 5 c.c. of 25 per cent solution produced a temporary decrease in sphincter resistance with a return to the original level after one or one and one-half minutes. Instillation of 20 c.c. of the same solution resulted in either an increase or no change in intramural resistance. Puestow<sup>189</sup> stated that magnesium sulfate had an inconstant stimulating effect upon the duodenal musculature in dogs, but no evident independent activity upon the orifice of the choledochus. Gantt and Volborth<sup>81</sup> observed that the introduction of magnesium sulfate solution into the duodenum of the dog was not followed by the expulsion of bile and that the drug did not have any constant effect upon the pressure within the gall bladder and bile ducts. Boyden and Birch<sup>43, 44</sup> noted that magnesium sulfate given by mouth or by duodenal tube to cats did not induce emptying of the gall bladder.

In one human subject, Ivy, Voegtlin, and Greengard<sup>114</sup> apparently relieved spasm of the sphincter (which had been provoked by the intravenous injection of a secretin-cholecystokinin mixture) by the instillation of magnesium sulfate into the duodenum. Doubilet and Colp<sup>68</sup> and Best and Hicken<sup>27</sup> also reported sphincter relaxation following the administration of magnesium sulfate in man.

Bergh and Layue<sup>17</sup> observed that a 12.5 Gm. dose of magnesium sulfate may produce any one of four types of effects upon the sphincter of the common bile duct in man. It may produce relaxation with or without an initial contraction, it may produce an initial contraction followed by a return to the original tonus level, or there may be no effect. Sphincter relaxation occurred thirty-three times in a series of forty-two observations. The relaxation, however, frequently was preceded by a temporary increased intramural resistance.

There has been some question as to the effectiveness of the oral route of administration of magnesium sulfate as compared to duodenal instillation. Meltzer<sup>161</sup> stated that the salt is ineffective when given by mouth. Eppinger<sup>22</sup> also advised duodenal instillation of the drug.

*Nitroglycerin (Glyceryl Trinitrate).*—In 1936 Best and Hicken<sup>22-26</sup> and Butsch, McGowan, and Walters<sup>55, 146</sup> independently described the relaxing effect of nitroglycerin upon the sphincter, showing that it produced a more prolonged, but less marked effect than amyl nitrite. Our observations were confirmatory. Nitroglycerin ( $\frac{1}{100}$  gr. tablet under the tongue) produced relaxation of the sphincter which was maintained for fifteen to sixty minutes in 6 of our 7 cases. In the other case a spasm of the sphincter occurred. Relief from biliary colic after the administration of nitroglycerin has been described by a number of clinicians.<sup>18-26, 55, 146, 147, 175, 215, 226-234</sup>

*Erythrol Tetranitrate.*—The action of erythrol tetranitrate upon smooth muscle develops slowly but persists for long periods. It is desirable to know, therefore, whether this drug produces a prolonged relaxation of the sphincter of Oddi. Two experiments were carried out (using 1 gr. of erythrol tetranitrate by mouth), and in neither case did the drug produce any significant change in sphincter resistance.

*Theophyllin Ethylenediamine.*—Snell, McGowan, and Butsch<sup>215</sup> reported one patient in whom the intravenous injection of theophyllin ethylenediamine produced relaxation of the sphincter, and Butsch, McGowan, and Walters<sup>55</sup> demonstrated that this drug could decrease the intrabiliary pressure which had been increased by the administration of codeine. In 5 experiments (using 0.24 Gm. of the drug) we were unable to demonstrate any significant effect upon the sphincter resistance after the intravenous injection of theophyllin ethylenediamine, even though the original intramural resistances were as high as 20 cm. of water in 2 of our cases. We did not measure the effect of the drug in any case with a spastic sphincter.

*Trasentin (Diphenylacetyldiethylaminoethanol).*—Spier, Neuwelt, and Necheles<sup>216</sup> demonstrated that trasentin caused relaxation of the gall bladder of the dog, and assumed that it produced a similar relaxation of the sphincter of Oddi. Maedonald<sup>142</sup> stated that the drug would decrease sphincter tonus in human subjects. We measured the sphincter resistance in 5 patients after the intramuscular injection of 75 mg. doses of trasentin. In 2 of the cases there was no change in the intramural resistance, and in the remaining 3 instances the relaxation was slight.

*Papaverine.*—Papaverine is said to relax the tonus of smooth muscle without paralyzing contractility. However, in 3 experiments we found that it did not influence the sphincter resistance when given in  $\frac{1}{2}$  gr. doses. Neither did it prevent the elevation of the intramural resistance following the administration of morphine. Similar findings have been reported by Butsch, McGowan, and Walters<sup>55</sup> and Doubilet and Colp.<sup>64</sup>

On the other hand, Reach<sup>155</sup> reported that it produced sphincter relaxation in the guinea pig, and Blass<sup>28</sup> stated that when papaverine was introduced into the duodenum of human subjects it caused a flow of

while others reported the opposite effect.<sup>44, 51</sup> Oddi<sup>178</sup> found that acid caused a contraction of the sphincter in animals. Archibald<sup>2</sup> reported similar findings. Jacobson and Gydeson<sup>116</sup> stated that the introduction of 0.4 per cent acid was followed by an initial sphincter contraction and increased intraductal pressure, but with a subsequent decrease. On the other hand, Cole,<sup>58</sup> Iwanaga,<sup>115</sup> and Giordano and Mann<sup>83</sup> observed that hydrochloric acid decreased the resistance of the sphincter.

In human subjects Doubilet and Colp<sup>68</sup> found that the instillation into the duodenum of 0.9 per cent hydrochloric acid caused a spasm of the sphincter. We have confirmed that observation in 1 case with 0.5 per cent acid.

*Histamine.*—Histamine, when injected subcutaneously, generally produces stimulation of the tone of smooth muscle, but the susceptibility of different muscles varies, and some are not affected at all. The intestinal muscle is only slightly affected, but the drug does produce some contraction of the gall bladder.<sup>94, 101, 169</sup>

The effect upon the sphincter of Oddi was studied in 6 experiments after the subcutaneous injection of 0.5 mg. histamine phosphate. In 3 patients there was no effect. In the other 3 there was relaxation, preceded in 1 case by an initial contraction.

Reach<sup>195</sup> reported that histamine exerted no significant effect upon the sphincter in guinea pigs. Lueth<sup>138</sup> found that it caused an increased intramural resistance in dogs. Butsch, McGowan, and Walters<sup>55, 147</sup> observed that, in man, the injection of 0.6 mg. histamine had no effect upon the pressure within the common bile duct.

*Epinephrine.*—Epinephrine has been reported to cause contraction, relaxation, or to have no effect upon the gall bladder.<sup>5, 32, 50, 57, 63, 94, 224</sup> It appears that its effect must be variable. There is a similar disparity in reports concerning its action upon the sphincter. McWhorter<sup>151</sup> reported that epinephrine increased the tension of the sphincter in dogs. Lueth<sup>138</sup> stated that it decreased the intramural resistance in doses of 1 to 5 c.c. of 1:10,000 solution, but that the opposite effect usually was obtained with smaller doses. Winkelstein and Aschner,<sup>244</sup> Iwanaga,<sup>115</sup> and Shi<sup>212</sup> reported relaxation of the sphincter in dogs following the administration of epinephrine. Kitakoji<sup>126</sup> stated that there was no significant effect from the drug. Butsch, McGowan, and Walters,<sup>55</sup> Best and Hicken,<sup>27</sup> and Doubilet and Colp<sup>68</sup> reported that, in man, there was little or no effect upon the sphincter following injections of epinephrine.

We studied the effect of epinephrine (10 minims of 1:1,000 solution subcutaneously) upon the sphincter of Oddi in 9 experiments. The results were variable. There was no significant effect in 2 cases; in 4 cases relaxation of the sphincter was produced; and in 3 cases injection of the drug was followed by an increased intramural resistance.

Dunn and Connell<sup>12</sup> disagreed, and stated that one would not expect inactivating change in the magnesium sulfate to occur during its passage through the stomach. Best and Hicken<sup>25</sup> noted that the drug produced a relaxation of the sphincter (as inferred from cholangiogram) when administered orally or intraduodenally. Bergh and Lavy<sup>1</sup> found that the relaxing effect of magnesium sulfate is similar whether the drug be given by mouth or administered intraduodenally. However, this relaxing effect is not great. It is less constant and weaker than the effect produced by amyl nitrite or by a fatty meal. Furthermore, the same authors in conjunction with Boyden<sup>133</sup> recently have found that magnesium sulfate acts primarily on the gall bladder and not on the sphincter in causing a flow of bile into the duodenum.

*Calcium Chloride and Calcium Gluconate.*—Eleven experiments were carried out to study the effect of the intravenous injection of 10 c.c. 10 per cent solutions of calcium chloride and calcium gluconate. The results were not constant. Contraction of the sphincter followed the injection of the drug in 3 cases, and slight relaxation occurred twice. In the remaining 6 patients there was no significant effect.

Butsch, McGowan, and Walters<sup>55</sup> reported that the intravenous injection of calcium chloride failed to lower the pressure within the bile duct in human patients. Winkelstein and Aschner<sup>244</sup> stated that the intraduodenal injection of this drug produced an increased tonus of the sphincter of Oddi in dogs.

Hoehman<sup>104</sup> and Lampson and Simeone<sup>131</sup> reported having observed patients in whom relief from biliary colic followed the intravenous injection of calcium salts. In the light of our experiments it seems unlikely that such relief could be due to relaxation of sphincter spasm. Neither is it likely that the relief is due to relaxation of the gall bladder, since it has been reported that calcium salts produce augmentation of tonus rhythm<sup>224</sup> and some evacuation<sup>32</sup> of that organ.

*Ethyl Alcohol.*—The effect upon sphincter resistance of the intraduodenal instillation of 15 to 25 c.c. of 95 per cent ethyl alcohol diluted to 50 c.c. with water was studied in 3 experiments. In 1 case there was no effect, and in each of the other 2 there was a very slight relaxation.

Nygaard<sup>175</sup> observed a patient with postcholecystectomy colic in whom the ingestion of alcohol initiated the pain. Butsch, McGowan, and Walters<sup>55</sup> stated that, in man, 30 c.c. of alcohol had no effect upon the pressure within the bile duct. Cole<sup>58</sup> reported that, in the dog, alcohol in the stomach usually produced no effect upon the sphincter resistance, but occasionally it caused a definite relaxation.

*Hydrochloric Acid.*—Reports concerning the effect of hydrochloric acid upon the sphincter of Oddi have been contradictory. A number of investigators reported that the application of dilute hydrochloric acid to the duodenal mucosa produced a discharge of bile,<sup>1, 115, 181, 199</sup>

relaxation of the sphincter of Oddi. Iwanaga,<sup>115</sup> Winkelstein and Aschner,<sup>244</sup> Kitakoji,<sup>126</sup> Lueth,<sup>138</sup> and Shi<sup>212</sup> reported relaxation of the sphincter in dogs after the administration of atropine. On the other hand, Reach<sup>195</sup> observed that the drug usually produced contraction of the sphincter in guinea pigs, and Cole<sup>58</sup> stated that it had no effect upon the sphincter resistance in dogs.

On the basis of animal experiments showing relaxation of the sphincter following the administration of atropine and contraction following the injection of pilocarpine, several investigators have inferred that the autonomic nervous system plays an important role in the regulation of sphincter activity in the dog. In man, however, we have observed that atropine and pilocarpine do not influence the intramural resistance. This suggests that the parasympathetic nervous system does not play an important part in the regulation of sphincter activity in human subjects.

*Acetyl-Beta-Methylcholine Chloride (Mecholyl).*—In 2 patients we studied the effect upon the sphincter of the subcutaneous injection of 15 and 20 mg. doses of acetyl-beta-methylcholine chloride. In 1 case a contraction of the sphincter followed the injection of the drug and persisted for more than thirty minutes. In the other, there was little change except for a short period of increased sphincter resistance.

Kitakoji<sup>126</sup> reported that acetylcholine caused contraction of the sphincter of Oddi in dogs. Lueth's<sup>138</sup> findings were similar, but were not constant. In two of his experiments the intramural resistance decreased, even though the intraduodenal pressure remained unchanged or increased. Butsch, McGowan, and Walters<sup>55</sup> observed no effect upon the intrabiliary pressure in man following administration of the drug.

*Pilocarpine.*—In 8 experiments we measured the effect of the subcutaneous injection of 6 mg. of pilocarpine upon the sphincter resistance in human subjects. In 7 patients there was no change in intramural resistance, and relaxation was produced in 1 case. The importance of this observation in relation to inferences concerning the mechanism of regulation of the sphincter activity already has been discussed.

In animals, on the other hand, pilocarpine causes contraction of both the gall bladder and the sphincter. Reach<sup>195</sup> was the first to study the effect of this drug upon the sphincter (1920). He observed that it caused a prompt contraction in guinea pigs. Winkelstein and Aschner,<sup>244</sup> Iwanaga,<sup>115</sup> Kitakoji,<sup>126</sup> Lueth,<sup>138</sup> and Shi<sup>212</sup> observed a similar effect upon the sphincter resistance in dogs.

Westphal noted that, in pregnant women studied by duodenal aspiration, the initial effect of pilocarpine was to inhibit the flow of bile. Subsequently there was a flow of dark bile. Westphal attributed that response to a temporary spasm of the sphincter of Oddi resulting from pilocarpine stimulation. Since that time, however, Tanturi and Ivy<sup>229</sup>



*Ephedrine*.—In 4 experiments the results of the subcutaneous injection of 50 mg. of ephedrine sulfate, like those following epinephrine, were variable. In 1 case the drug produced contraction of the sphincter, in another patient it caused a temporary relaxation, and there was no effect in the remaining 2 cases.

Butsch, McGowan, and Walters<sup>55</sup> and Best and Hicken<sup>23</sup> reported that ephedrine had no effect upon the human sphincter.

*Benzedrine Sulfate (Benzyl Methyl Carbinamine Sulfate)*.—Benzedrine has been reported to cause relaxation of the gall bladder in animals,<sup>78, 169</sup> and to have no effect upon the gall bladder in man.<sup>208</sup> There have been no reports concerning its action on the sphincter of Oddi.

The effect of the subcutaneous injection of 20 to 30 mg. of benzedrine sulfate was studied in 6 experiments. The results were somewhat variable, but indicated that the effect was probably insignificant.

*Caffeine Sodium Benzoate*.—In 8 experiments the subcutaneous injection of 7.5 Gm. of caffeine sodium benzoate was found to produce no significant effect upon the sphincter resistance.

Reach<sup>195</sup> stated that caffeine citrate produced contraction of the sphincter of Oddi in guinea pigs. Lueth,<sup>138</sup> on the other hand, reported that caffeine caused no change in the intramural resistance in dogs, while Iwanaga<sup>115</sup> stated that it produced relaxation in dogs and rabbits. Butsch, McGowan, and Walters<sup>55</sup> reported that caffeine sodium benzoate produced no effect upon the sphincter in human subjects.

*Atropine*.—In 11 experiments we studied the effect of the subcutaneous administration of atropine sulfate in doses of  $\frac{1}{50}$  to  $\frac{1}{100}$  gr. In 10 cases there was no significant change in the intramural resistance, and in 1 case the resistance was slightly decreased.

Clinicians have assumed that atropine paralyzes the innervation of the smooth muscle of the sphincter of Oddi, causing relaxation, but there is little evidence that this actually occurs in man. Volini and O'Brien<sup>225</sup> have pointed out that atropine almost always fails to relieve biliary colic.

Butsch, McGowan, and Walters<sup>55</sup> found no effect from atropine upon the sphincter in man. Doubilet and Colp<sup>68</sup> stated that the drug does not inhibit sphincter spasm following the injection of morphine, but that it does prevent spasm following the intraduodenal instillation of hydrochloric acid. They also reported one case with an irritable sphincter in which atropine seemed to decrease the irritability. Pribram<sup>188</sup> reported a patient in whom cholangiography showed a spastic sphincter with no emptying for almost an hour. After the intravenous administration of 1 mg. of atropine, a roentgenogram showed the contrast medium to be flowing into the duodenum.

The preponderance of evidence, including our own, indicates that atropine does not cause the human sphincter to relax. Most experimenters agree that in animals, on the contrary, atropine does produce

relaxation of the sphincter of Oddi. Iwanaga,<sup>115</sup> Winkelstein and Aselmer,<sup>244</sup> Kitakoji,<sup>126</sup> Lueth,<sup>138</sup> and Shi<sup>212</sup> reported relaxation of the sphincter in dogs after the administration of atropine. On the other hand, Reach<sup>195</sup> observed that the drug usually produced contraction of the sphincter in guinea pigs, and Cole<sup>56</sup> stated that it had no effect upon the sphincter resistance in dogs.

On the basis of animal experiments showing relaxation of the sphincter following the administration of atropine and contraction following the injection of pilocarpine, several investigators have inferred that the autonomic nervous system plays an important role in the regulation of sphincter activity in the dog. In man, however, we have observed that atropine and pilocarpine do not influence the intramural resistance. This suggests that the parasympathetic nervous system does not play an important part in the regulation of sphincter activity in human subjects.

*Acetyl-Beta-Methylcholine Chloride (Meccholy).*—In 2 patients we studied the effect upon the sphincter of the subcutaneous injection of 15 and 20 mg. doses of acetyl-beta-methylcholine chloride. In 1 case a contraction of the sphincter followed the injection of the drug and persisted for more than thirty minutes. In the other, there was little change except for a short period of increased sphincter resistance.

Kitakoji<sup>126</sup> reported that acetylcholine caused contraction of the sphincter of Oddi in dogs. Lueth's<sup>138</sup> findings were similar, but were not constant. In two of his experiments the intramural resistance decreased, even though the intraduodenal pressure remained unchanged or increased. Butsch, McGowan, and Walters<sup>7</sup> observed no effect upon the intrabiliary pressure in man following administration of the drug.

*Pilocarpine.*—In 8 experiments we measured the effect of the subcutaneous injection of 6 mg. of pilocarpine upon the sphincter resistance in human subjects. In 7 patients there was no change in intramural resistance, and relaxation was produced in 1 case. The importance of this observation in relation to inferences concerning the mechanism of regulation of the sphincter activity already has been discussed.

In animals, on the other hand, pilocarpine causes contraction of both the gall bladder and the sphincter. Reach<sup>19</sup> was the first to study the effect of this drug upon the sphincter (1920). He observed that it caused a prompt contraction in guinea pigs. Winkelstein and Aselmer,<sup>244</sup> Iwanaga,<sup>11</sup> Kitakoji,<sup>127</sup> Lueth,<sup>138</sup> and Shi<sup>21</sup> observed a similar effect upon the sphincter resistance in dogs.

Westphal noted that, in pregnant women studied by duodenal aspiration, the initial effect of pilocarpine was to inhibit the flow of bile. Subsequently there was a flow of dark bile. Westphal attributed that response to a temporary spasm of the sphincter of Oddi resulting from pilocarpine stimulation. Since that time, however, Tanturi and Ivy<sup>221</sup>

have demonstrated that pilocarpine causes first an inhibition and then a stimulation of the secretion of bile, so Westphal's observations could be explained without considering any activity of the sphincter.

*Prostigmine (Dimethyl Carbamic Ester of Oxyphenyl-Trimethyl-Ammonium Methyl Sulfate).*—Tanturi and Ivy<sup>220</sup> reported that prostigmine caused a primary inhibition of bile secretion, lasting five to ten minutes, followed by stimulation. There has been no information concerning its effect upon the sphincter.

In 6 experiments we observed that the subcutaneous injection of 1 c.c. of 1:4,000 solution of prostigmine did not influence the sphincter of Oddi in 4 of the human subjects. Sphincter relaxation followed injection of the drug in 1 patient, and in 1 case there was slight sphincter contraction.

*Posterior Pituitary Extract.*—Lueth<sup>128</sup> and Shi<sup>213</sup> reported that posterior pituitary extract caused relaxation of the sphincter of Oddi in dogs, while Cole<sup>58</sup> stated that it produced an increase in the sphincter resistance.

In 4 human subjects we observed no significant effect upon the sphincter after the subcutaneous injection of posterior pituitary extract (1 c.c. pituitrin).

#### SUMMARY

Anatomists have demonstrated a distinct sphincter of the common bile duct, and physiologic studies have indicated that it can function independently of the intestinal musculature. In addition to the action of the intrinsic sphincter, it is possible that duodenal motility and tone may influence the resistance to bile flow. However, in man the anatomical arrangement of the window in the duodenal muscle through which the bile duct enters the intestine is such that duodenal peristalsis probably exerts a minimal effect.

Functions which have been attributed to the sphincter of Oddi are: (1) making possible the filling of the gall bladder, (2) preventing the regurgitation of intestinal contents into the bile duct, (3) regulating the discharge of bile into the duodenum, and (4) erecting the papilla.

The discharge of bile into the duodenum is dependent upon the tonus of the sphincter, the activity of the gall bladder, and the pressure of bile secretion. In order to secure information concerning the effect of various types of stimulation upon the sphincter mechanism, the resistance to the flow of fluid may be studied in patients with intubation of the common bile duct.

Since there is no method allowing measurement of the sphincter resistance in entirely normal human subjects, we have considered the figures obtained in individuals who had recovered from their operations, who were feeling well, and who had fasted for periods of six or eight hours, as "normal." In such cases the sphincter withstands

pressures between 9 and 23 cm. of water. and usually the sphincter resistance is around 12 to 15 cm. of water

Changes of a few millimeters in the intraductal pressure occur during respiration, and marked changes occur during coughing, laughing, or vomiting as a result of a temporary increase in intra-abdominal pressure. Even when the sphincter resistance appears to be stabilized, changes of several centimeters' resistance may occur spontaneously from time to time.

In some patients the sphincter remains irritable for weeks after removal of a calculus from the common bile duct. In such instances the muscle readily goes into spasm. After prolonged external drainage of the bile duct, the irritability usually disappears and the sphincter returns to "normal."

The ingestion of a fatty meal consisting of egg yolks and cream causes relaxation of the sphincter: proteins occasionally produce relaxation, but neither a carbohydrate meal nor glucose given intravenously has any significant effect. Water taken by mouth also fails to produce a change in sphincter resistance.

Morphine, codeine, pantopon, and dilaudid cause contraction of the sphincter of Oddi.

Amyl nitrite and nitroglycerin produce relaxation of the sphincter, but atropine does not. Erythrol tetranitrate is ineffective. Trasentin, epinephrine, ephedrine, histamine, and ethyl alcohol sometimes produce sphincter relaxation, but the effects are variable.

Magnesium sulfate may produce sphincter relaxation with or without an initial contraction; it may produce an initial contraction followed by a return to the original tonus level, or there may be no effect. Relaxation, when it does occur, usually is not great, and contraction of the gall bladder following administration of magnesium sulfate probably is more important than sphincter relaxation in producing a flow of bile into the duodenum in patients with a functioning gall bladder.

Atropine, pilocarpine, papaverine, posterior pituitary extract, benzedrine, prostigmine, caffeine sodium benzoate, and theophyllin ethylenediamine have no significant effect upon the sphincter. The effects of sodium dehydrocholate, histamine, epinephrine, ephedrine, calcium gluconate and calcium chloride are not constant.

Severance of the nerves in the hepatoduodenal ligament is not recommended as a means of lowering sphincter resistance.

#### REFERENCES

1. Auster, L. S., and Crohn, B. B.: Notes on Studies in the Physiology of the Gallbladder, *Am. J. M. Sc.* 164: 345, 1922.
2. Archibald, E.: The Experimental Production of Pancreatitis in Animals as the Result of the Resistance of the Common Duct Sphincter, *Surg., Gynec. & Obst.* 28: 529-545, 1919.
3. Buchrach, W. H., and Fogelson, S. J.: Cholecystojejunostomy, *SURGERY* 6: 882-892, 1939.

4. Baggenstoss, A. H.: Major Duodenal Papilla: Variations of Pathologic Interest and Lesions of the Mucosa, *Arch. Path.* 26: 873 868, 1938.
5. Bainbridge, P. A., and Dale, H. H.: The Contractile Mechanism of the Gall Bladder and Its Intrinsic Nervous Control, *J. Physiol.* 33: 138 155, 1905 1906.
6. Benson, K. W.: Dilatation of the Bile Ducts and Its Relation to Distress After Cholecystectomy, *Am. J. Digest. Dis.* 7: 1-2, 1940.
7. Berg, B. N.: Gall-Bladder Function After Division of the Common Duct and Transplantation of the Proximal Segment, *Surg., Gynec. & Obst.* 46: 464-469, 1928.
8. Berg, J.: Studien über die Funktion der Gallenwege unter normalen und gewissen abnormen Verhältnissen, *Acta. chir. Scandinav. (suppl.)* 2: 1-185, 1922.
9. Bergh, G. S.: The Common Bile Duct, *Staff Meet. Bull. Univ. of Minnesota Hosp.* 10: 73 93, 1938.
10. Bergh, G. S.: Discussion, *Minnesota Med.* 21: 877, 1938.
11. Bergh, G. S.: The Sphincter Mechanism of the Common Bile Duct in Human Subjects: Its Reaction to Certain Types of Stimulation, Doctor's Thesis, University of Minnesota, 1940.
12. Bergh, G. S.: The Effect of Food Upon the Sphincter of Oddi in Human Subjects, *Am. J. Digest. Dis.* 9: 40 43, 1942.
13. Bergh, G. S., and Layne, J. A.: A Study of Visceral Pain as Related to the Biliary Tract, *Proc. Soc. Exper. Biol. & Med.* 38: 44 45, 1938.
14. Bergh, G. S., and Layne, J. A.: A Demonstration of the Independent Contraction of the Sphincter of the Common Bile Duct in Human Subjects, *Am. J. Physiol.* 128: 690 694, 1940.
15. Bergh, G. S., and Layne, J. A.: The Effect of Magnesium Sulphate Upon the Sphincter of Oddi of Man, *Am. J. Digest. Dis.* In press.
16. Bergh, G. S., Sandblom, P., and Ivy, A. C.: Effects of Removal of the Functioning Gall Bladder, *Surg., Gynec. & Obst.* 62: 811 814, 1936.
17. Bernhard, F.: Die Bedeutung der Cholangiographie für Praxis und Forschung, *Chirurg* 9: 201 208, 1937.
18. Best, R. R.: Cholangiographic Demonstration of the Remaining Common Duct Stone and Its Non Operative Management, *Surg., Gynec. & Obst.* 66: 1040 1046, 1938.
19. Best, R. R.: Increased Bile Flow and Pressure as an Aid in the Surgical and Non Surgical Management of Biliary Tract Disease, *Minnesota Med.* 21: 877, 1938.
20. Best, R. R.: Biliary Flush as an Aid in the Surgical and Non Surgical Management of Biliary Tract Disease, *Rocky Mountain M. J.* 36: 319 323, 1939.
21. Best, R. R., and Hicken, N. F.: Biliary Dyssynergia: Physiological Obstruction of the Common Bile Duct, *Surg., Gynec. & Obst.* 61: 721 734, 1935.
22. Best, R. R., and Hicken, N. F.: Biliary Dyssynergia: Cholangiographic Recognition and Its Significance, *West J. Surg.* 44: 467 473, 1936.
23. Best, R. R., and Hicken, N. F.: Cholangiographic Demonstration of Biliary Dyssynergia and Other Obstructive Lesions of the Gallbladder and Bile Ducts, *J. A. M. A.* 107: 1615 1619, 1936.
24. Best, R. R., and Hicken, N. F.: Nonoperative Management of Remaining Common Duct Stones, *J. A. M. A.* 110: 1257 1261, 1938.
25. Best, R. R., and Hicken, N. F.: The Therapeutic Value of Glycerol Trinitrate in Biliary Colic and in the Post Operative Phase of Biliary Tract Disease, *Am. J. Surg.* 39: 533 537, 1938.
26. Best, R. R., Hicken, N. F., and Finlayson, A. I.: The Effect of Dehydrocholic Acid Upon Biliary Pressure and Its Clinical Application, *Ann Surg.* 110: 67 80, 1939.
27. Bianchi, J. B.: Historia Hepatice (1711), cited by Boyden.<sup>26</sup>
28. Blass, G.: Ueber die Behandlung der sogenannten Pseudoreizide nach Cholezystektomie, *Wien kln. Wchnschr.* 41: 1429 1430, 1928.
29. Blond, K.: Zur Gallenblasenphysiologie und—Pathologie, *Klin. Wchnschr.* 6: 1606 1608, 1927.
30. Bottin, J.: Le reflux duodéno cholédocien et la nécrose aiguë du pancreas, *Rev. belge sc. méd.* 11: 125 152, 1939.
31. Boyden, E. A.: The Effect of Natural Foods on the Distention of the Gall Bladder, With a Note on the Change in Pattern of the Mucosa as It Passes From Distention to Collapse, *Anat. Rec.* 30: 333 363, 1925.

32. Boyden, E. A.: A Study of the Behavior of the Human Gall Bladder in Response to the Ingestion of Food; Together With Some Observations on the Mechanism of the Expulsion of Bile in Experimental Animals, *Anat. Rec.* 33: 201-255, 1926.
33. Boyden, E. A.: Behavior of Human Gall-Bladder During Fasting and in Response to Food, *Proc. Soc. Exper. Biol. & Med.* 24: 157-162, 1926.
34. Boyden, E. A.: Gall Bladder Versus Sphincter Papillae, *Proc. Soc. Exper. Biol. & Med.* 25: 99-100, 1927.
35. Boyden, E. A.: An Analysis of the Reaction of the Human Gall Bladder to Food, *Anat. Rec.* 40: 147-191, 1928.
36. Boyden, E. A.: The Pars Intestinalis of the Common Bile Duct as Viewed by the Older Anatomists (Vesalius, Glisson, Bianchi, Vater, Haller, Santorini, etc.), *Anat. Rec.* 66: 217-232, 1936.
37. Boyden, E. A.: The Sphincter of Oddi in Man and Certain Representative Mammals, *SURGERY* 1: 25-37, 1937.
38. Boyden, E. A.: Discussion, *Minnesota Med.* 21: 877, 1938.
39. Boyden, E. A.: The Extrahepatic Biliary Tract as a Functional Unit, *SURGERY* 3: 260-261, 1938.
40. Boyden, E. A.: The Sphincter of Oddi, *SURGERY* 9: 443-446, 1941.
41. Boyden, E. A.: Hypertrophy of the Sphincter Choledochus: A Cause of Internal Biliary Fistula, *SURGERY* 10: 567, 1941.
42. Boyden, E. A., and Birch, C. L.: Conditions Affecting the Emptying-Time of the Human Gall Bladder, *Proc. Soc. Exper. Biol. & Med.* 24: 827-831, 1927.
43. Boyden, E. A., and Birch, C. L.: Emptying of Human Gall Bladder After Saline Cathartics, *Proc. Soc. Exper. Biol. & Med.* 25: 840-842, 1928.
44. Boyden, E. A., and Birch, C. L.: Reaction of the Gall Bladder to Stimulation of Gastro-Intestinal Tract, I. Response to Substances Injected Into the Duodenum, *Am. J. Physiol.* 92: 287-300, 1930.
45. Boyden, E. A., and Johnson, F. E.: Unpublished data.
46. Boyden, E. A., and Parmacek, L.: Reflex Inhibition of the Human Gall Bladder, *Proc. Soc. Exper. Biol. & Med.* 25: 462-464, 1928.
47. Boyden, E. A., and Rigler, L. G.: A Cholecystographie and Fluoroscopic Study of the Reaction of the Human Gall Bladder to Faradic Stimulation of the Stomach and Duodenum, *Anat. Rec.* 59: 427-447, 1934.
48. Boyden, E. A., and Saunders, A. M.: Duodenal Drainage of the Human Gall Bladder, *Proc. Soc. Exper. Biol. & Med.* 25: 458, 1928.
49. Brendolan, G.: Conseguenze prossime e remote della sezione della sfintere di Oddi, *Arch. ital. di chir.* 40: 529, 1935.
50. Brugsch, T., and Horstner, H.: Chologagie und Cholagogie, *Arch. f. exper. Path. u. Pharmacol.* 118: 267-312, 1926-1927.
51. Bruno, G. G.: L'excitabilité spécifique de la muqueuse du tube digestif. Sixième mémoire. La bile comme agent digestif, *Arch. d. se. biol. St. Petersbourg* 7: 87-142, 1899.
52. Burget, G. E.: The Regulation of the Flow of Bile. II. Effect of Eliminating the Sphincter of Oddi, *Am. J. Physiol.* 79: 130-134, 1926.
53. Burget, G. E.: The Regulation of the Flow of Bile. III. The Role of the Gall Bladder, *Proc. Soc. Exper. Biol. & Med.* 24: 583-585, 1927.
54. Burget, G. E., and Brockelhurst, R. J.: An Undescribed Bile-Expelling Mechanism in the Guinea Pig, *Proc. Soc. Exper. Biol. & Med.* 24: 843-845, 1927.
55. Butsch, W. L., McGowan, J. M., and Walters, W.: Clinical Studies on the Influence of Certain Drugs in Relation to Biliary Pain and to the Variations in Intrabiliary Pressure, *Surg., Gynec. & Obst.* 63: 451-456, 1936.
56. Carter, R. F.: When to Remove the Drainage Tube in Common Bile Duct Drainage, *Surg., Gynec. & Obst.* 63: 163-169, 1936.
57. Chiray, M., and Pavel, I.: Comment la vésicule biliaire se remplit et comment elle se vide. Rapports fonctionnels de la vésicule et du sphincter d'Oddi, *Presse méd.* 1: 289-291, 1928.
58. Cole, W. H.: Relation of Gastric Content to the Physiology of the Common Duct Sphincter, *Am. J. Physiol.* 72: 39-42, 1925.
59. Colp, R., and Douillet, H.: Endocholedochal Sphincterotomy, *Surg., Gynec. & Obst.* 66: 882-888, 1938.
60. Colp, R., Douillet, H., and Gerber, I. E.: Endocholedochal Section of the Sphincter of Oddi, *Arch. Surg.* 33: 696-707, 1936.
61. Copher, G. H., and Kodama, S.: The Regulation of the Flow of Bile and Pancreatic Juice Into the Duodenum, *Arch. Int. Med.* 38: 647-653, 1926.



90. Grebe, A.: Erweiterung unserer Kenntnis über die Wirkung "ruhigstellender" Pharmaka auf die Funktion des extrahepatischen Gallenwegsystems, *Ztschr. f. klin. Med.* 115: 446-453, 1930-1931.
91. Haberer, H., and Clairmont, P.: Experimentelle Untersuchungen über das Verhalten des Cysticusstumpfes nach der Cholecystectomy, *Arch. f. klin. Chir.* 73: 679, 1904.
92. Haberland, H. F. O.: Die Bedeutung des Entleerungsmechanismus der Gallenblase für die Praxis, *Ztschr. f. d. ges. exper. Med.* 105: 303, 1939.
93. Halpert, B.: The Choledochoduodenal Junction. A Morphologic Study in the Dog, *Anat. Rec.* 53: 83-102, 1932.
94. Halpert, B., and Lewis, J. H.: Experiments on the Isolated Whole Gall Bladder of the Dog, *Am. J. Physiol.* 93: 506-520, 1930.
95. Halpert, B., Rewbridge, A. G., and Henley, C.: Effects of Cholecystectomy on the Biliary System. A Morphologic Study in the Dog, *Arch. Surg.* 26: 589-601, 1933.
96. Hayashi, I., and Kitakoji, Y.: Studien über die Funktionen der Gallenblase und des Oddischen Muskels in Bezug auf die Absonderung der Blasengalle. III. Mitteilung. Über den Einfluss von gallenaustreibenden Substanzen auf die Funktionen der Gallenblase und des Oddischen Muskels, *Nagoya J. M. Sc.* 5: 75, 1931.
97. Hecht, P., and Mantz, J.: Ueber die klinische Brauchbarkeit der Duodenalsonde bei Erkrankungen der Gallenwege, *Deutsche med. Wchnschr.* 48: 418-419, 1922.
98. Helly, K. K.: Die Schliessmuskulatur an den Mündungen des Gallen- und der Pankreasgange, *Arch. f. mikroskop. Anat.* 54: 614, 1899.
99. Hendrickson, W. P.: A Study of the Musculature of the Entire Extrahepatic Biliary System, Including That of the Duodenal Portion of the Common Bile Duct and of the Sphincter, *Bull. Johns Hopkins Hosp.* 9: 221, 1898.
100. Heiken, N. T., Best, R. R., and Hunt, H. B.: Cholangiography: Visualization of the Gall Bladder and Bile Ducts During and After Operation, *Ann. Surg.* 103: 210-229, 1936.
101. Higgins, G. M., Deissler, K., and Mann, F. C.: Tonus Rhythm in the Isolated Gall Bladder and the Effect of Certain Drugs, *Am. J. Physiol.* 112: 461-467, 1935.
102. Higgins, G. M., and Mann, F. C.: A Physiologic and Anatomic Consideration of the Sphincteric Mechanism of the Choledochus, *Anat. Rec.* 35: 13, 1927.
103. Hill, H. A.: Functional Disorders of the Extrahepatic Biliary System. Biliary Dys-synergia or Dyskinesia, *Radiol.* 29: 261-278, 1937.
104. Hochman, C. H.: Nonnarcotic Control of Pain in Biliary Colic, *M. Rec.* 144: 559, 1936.
105. Horrall, O. H.: Bile: Its Toxicity and Relation to Disease, Chicago, 1938, University of Chicago Press.
106. Ivy, A. C.: The Physiology of the Gall Bladder, *Physiol. Rev.* 14: 1-102, 1934.
107. Ivy, A. C.: The Etiology and Therapy of Biliary Tract Disease From the Viewpoint of Applied Physiology, *Ohio State M. J.* 32: 1155-1159, 1936.
108. Ivy, A. C.: Gallbladder and Bile Ducts, in *Portis, S. A.: Diseases of the Digestive System*, Philadelphia, 1941, Lea & Febiger.
109. Ivy, A. C., and Burgh, G. S.: The Applied Physiology of the Extrahepatic Biliary Tract, *J. A. M. A.* 103: 1500-1504, 1934.
110. Ivy, A. C., and Goldman, L.: Physiology of the Biliary Tract, *J. A. M. A.* 113: 241, 2417, 1939.
111. Ivy, A. C., and Oldberg, E.: Contraction and Evacuation of Gall Bladder Caused by Highly Purified "Secretin" Preparation, *Proc. Soc. Exper. Biol. & Med.* 25: 113-115, 1927.
112. Ivy, A. C., Oldberg, E., Kloster, G., and Luth, H. C.: A Hormone Mechanism for Gall Bladder Contraction and Evacuation. Physiological and Chemical Studies, *Am. J. Physiol.* 85: 381-384, 1928.
113. Ivy, A. C., and Sundblom, P.: Biliary Dyskinesia, *Ann. Int. Med.* 8: 115-122, 1934.
114. Ivy, A. C., Vogtlin, W. L., and Greengard, H.: The Physiology of the Common Bile Duct. A Singular Observation, *J. A. M. A.* 100: 1319-1320, 1927.
115. Iwano, H.: Experimentelle Studien über den Mechanismus der Gallenausscheidung, insbesondere über die Funktion des Oddischen Sphinkters, *Mits. d. 1. Fakult. d. 1. Kyushu Universität* 10: 1-64, 1925.



116. Jacobson, C., and Gydeson, C.: *The Function of the Gallbladder in Biliary Flow*, Arch. Surg. 5: 374-394, 1922.
117. Jastrow, M.: *The Liver in Antiquity and the Beginnings of Anatomy*, Univ. Pennsylvania M. Bull. 20: 238-245, 1908.
118. Joh, T. T.: *The Anatomy of the Duodenal Portion of the Bile and Pancreatic Ducts*, Anat. Rec. 32: 212, 1926.
119. Johnson, F. E.: *Effect Upon the Biliary Tract of Sectioning the Splanchnic Nerves*, Proc. Soc. Exper. Biol. & Med. 47: 399-400, 1941.
120. Judd, E. S.: *Condition of the Common Duct After Cholecystectomy*, J. A. M. A. 81: 704, 1923.
121. Judd, E. S., and Mann, F. C.: *The Effect of Removal of the Gall-Bladder: An Experimental Study*, Surg., Gynec. & Obst. 24: 437-442, 1917.
122. Jung, F. T., and Greengard, H.: *Response of the Isolated Gall Bladder to Cholecystokinin*, Am. J. Physiol. 103: 275-278, 1933.
123. Kalk, H., and Schöndube, W.: *Ueber die Funktion der Gallenblase. Untersuchungen an Normalen an Hand der Pituitrin—bzw. Hypophysinprobe*, Ztschr. f. d. ges. exper. Med. 53: 461-483, 1926-1927.
124. Kaufmann, J.: *The Role of Spasticity in Diseases of the Digestive Tract. A Case of Visceral Tetany, Causing Acute Cholangitis and Pancreatitis*, Am. J. M. Sc. 166: 67-80, 1923.
125. Kipp, H. A.: *Observations on the Variations in Bile Pressure in the Human Biliary Tract*, J. A. M. A. 106: 2223-2227, 1936.
126. Kitakoji, Y.: *Studien über die Funktionen der Gallenblase und des Oddischen Muskels in Bezug auf die Absonderung der Blasengalle. I. Mitteilung. Über den Einfluss von Nervengiften auf die Funktionen der Gallenblase und des Oddischen Muskels*, Nagoya J. M. Sc. 5: 24, 1930.
127. Klee, P., and Klupfel, O.: *Experimenteller Beitrag zur Funktion der Gallenblase*, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 27: 785, 1914.
128. Kreilkamp, B. L., and Boyden, E. A.: *Variability in the Composition of the Sphincter of Oddi: A Possible Factor in the Pathologic Physiology of the Biliary Tract*, Anat. Rec. 76: 485-497, 1940.
129. Krueger, H.: *The Action of Morphine on the Digestive Tract*, Physiol. Rev. 17: 618-645, 1937.
130. Künsztler, M.: *Vikariierende Funktionen bei ausgeschalteter Gallenblase*, Wien. med. Wchnschr. 84: 517-519, 1934.
131. Lampson, R. S., and Simeone, F. A.: *Intravenous Calcium Chloride and Its Use for the Relief of Visceral Colic: A Clinical and Experimental Study*, Surg., Gynec. & Obst. 66: 975-978, 1938.
132. Layne, J. A., and Bergh, G. S.: *An Experimental Study of Pain in the Human Biliary Tract Induced by Spasm of the Sphincter of Oddi*, Surg., Gynec. & Obst. 70: 18-24, 1940.
133. Layne, J. A., Boyden, E. A., and Bergh, G. S.: *The Effect of Magnesium Sulphate Upon the Gallbladder*. Unpublished data.
134. Letulle, M., and Nattan-Larrier: *Région vaticienne du duodénum et ampoule de Vater*, Bull. de la Soc. nat. de Paris 73: 491-506, 1898.
135. Leven, N. L.: *Reflux Into the Major Pancreatic Duct During Cholangiography*, Proc. Soc. Exper. Biol. & Med. 38: 808-809, 1938.
136. Lieb, C. C., and McWhorter, J. E.: *Action of Drugs on the Isolated Gall Bladder*, J. Pharmacol. & Exper. Therap. 7: 83-98, 1915.
137. Liek, E.: *Misserfolge nach Gallensteinoperationen*, Arch. f. klin. Chir. 128: 118-140, 1924.
138. Lueth, H. C.: *Studies on the Flow of Bile Into the Duodenum and the Existence of a Sphincter of Oddi*, Am. J. Physiol. 99: 237-252, 1931.
139. Lütken, U.: *Aufbau und Funktion der extrahepatischen Gallenwege*, Leipzig, 1926, F. C. W. Vogel.
140. Lyon, B. B. V.: *Diagnosis and Treatment of Diseases of the Gallbladder and Biliary Ducts. Preliminary Report on a New Method*, J. A. M. A. 73: 980-982, 1919.
141. Lyon, B. B. V.: *Diagnosis and Management of Gall Tract, Particularly Gall-Bladder, Disease*, Am. J. Digest. Dis. 1: 18-28, 1934.
142. Macdonald, D.: *Postoperative Perfusion of the Biliary Ductal System*, Canad. M. A. J. 43: 411-418, 1940.
143. MacDonald, I. G.: *The Histology of the Biliary Ducts and Its Correlation With the Symptomatology of Common Duct Stone*, Surg., Gynec. & Obst. 60: 775-780, 1935.

144. McClure, C. W.: *Functional Activities of the Pancreas and Liver*, New York, 1937, Medical Authors' Publishing Co.
145. McGowan, J. M., and Baker, J. O.: The Relation of Pregnancy to Biliary Disease and the Control of the Vomiting of Pregnancy, *Canad. M. A. J.* 39: 133-137, 1938.
146. McGowan, J. M., Butsch, W. L., and Walters, W.: The Use of Glyceryl Trinitrate (Nitroglycerin) for the Control of Pain Following Cholecystectomy, *Ann. Surg.* 104: 1013-1018, 1936.
147. McGowan, J. M., Butsch, W. L., and Walters, W.: Pressure in the Common Bile Duct of Man: Its Relation to Pain Following Cholecystectomy, *J. A. M. A.* 106: 2227-2230, 1936.
148. McGowan, J. M., and Henderson, F. F.: Prevention and Management of Pain Following Cholecystectomy, *New England J. Med.* 222: 948-953, 1940.
149. McGowan, J. M., Knepper, P. A., Walters, W., and Snell, A. M.: The Relation of Spasm of the Second Portion of the Duodenum to Biliary Colic, *Surg., Gynec. & Obst.* 66: 979-987, 1938.
150. McMaster, P. D., and Elman, R.: On the Expulsion of Bile by the Gall-bladder; and a Reciprocal Relationship With the Sphincter Activity, *J. Exper. Med.* 44: 173, 1926.
151. McWhorter, G. L.: The Surgical Significance of the Common Bile-Duct Sphincter, *Surg., Gynec. & Obst.* 32: 124-130, 1921.
152. Mann, F. C.: The Function of the Gall-Bladder. An Experimental Study, *New Orleans M. & S. J.* 71: 80, 1918.
153. Mann, F. C.: A Study of the Tonicity of the Sphincter at the Duodenal End of the Common Bile Duct, *J. Lab. & Clin. Med.* 5: 107-110, 1919.
154. Mann, F. C.: A Comparative Study of the Anatomy of the Sphincter at the Duodenal End of the Common Bile-Duct With Special Reference to Species of Animals Without a Gall-Bladder, *Anat. Rec.* 18: 355, 1920.
155. Mann, F. C.: The Functions of the Gallbladder, *Physiol. Rev.* 4: 251-273, 1924.
156. Mann, F. C., and Giordano, A. S.: The Bile Factor in Pancreatitis, *Arch. Surg.* 6: 130, 1923.
157. Mann, F. C., and Higgins, G. M.: A Physiologic Consideration of the Sphincter of the Ductus Choledochus, *Proc. Soc. Exper. Biol. & Med.* 24: 533, 1927.
158. Mann, F. C., and Higgins, G. M.: Emptying of Gall Bladder and Mechanism of Common Bile Duct of Guinea Pig, *Proc. Soc. Exper. Biol. & Med.* 24: 931-933, 1927.
159. Matsuno, Y.: Ueber die Muskulatur des Ductus Choledochus, *Virchows Arch. f. path. Anat.* 247: 208-215, 1923.
160. Meltzer, S. J.: The Disturbance of the Law of Contrary Innervation as a Pathogenetic Factor in the Diseases of the Bile Ducts and the Gall-Bladder, *Am. J. M. Sc.* 153: 469-477, 1917.
161. Mirizzi, P.: La cholecystectomie sans drainage, Paris, 1933, Masson et Cie.
162. Mirizzi, P. L.: Der normale grosse Gallengang, *Chirurg.* 18: 657-661, 1939.
163. Mirizzi, P. L.: Il sistema del hepatico: Su fisiopatologia, *Prensa méd. argent.* 28: 58-68, 1941.
164. Morgan, J. E.: De sedibus et causis morborum per anatomen indagatis libere quinque (1761), translated from the Latin by Benjamin Alexander, London, 1769, A. Millar and T. Cadell. Reprinted in part *M. Classics* 4: 610-837, 1940.
165. Morgan, J. E., Crandall, L. A., and Ivy, A. C.: Gall Bladder Evacuation by Egg Yolk in Stomach, *Proc. Soc. Exper. Biol. & Med.* 29: 227, 1931.
166. Murakami, T., and Uchiyama, H.: Functions of the Extrahepatic Bile Ducts and Secretory Function of the Liver, *Arch. Surg.* 42: 693-711, 1941.
167. Nagai, K., and Sawada, T.: Studies on Oddi's Sphincter and the Relation Between the Pancreatic Duct and the Common Bile Duct of Japanese, *Acta scholae med. univ. imp. in Kioto* 8: 91-101, 1925-1926.
168. Nakashima, K.: Studies on the Mode of Bile Outflow. V. About Oddi's Sphincter, the Regulator of the Bile Outflow, *Acta scholae med. univ. imp. Kioto* 9: 357-366, 1926-1927.
169. Necheles, H.: A Study of Gall Bladder Function, *Am. J. Digest. Dis.* 5: 568-571, 1938.
170. Neubauer, E.: Ueber Chologoga und ihre Wirkung auf die Gallensekretion, *Klin. Wochenschr.* 4: 926-930, 1925.

171. Newcomer, N. B., and Newcomer, E.: Further Discussion of the Relations of the Antrum and Cap to the Gall Bladder as Factors in Emptying the Gall Bladder, *Radiol.* 25: 547-565, 1935.
172. Newman, C.: Physiology of the Gall-Bladder and Its Functional Abnormalities, *Lancet* 1: 785-791, 1933.
173. Nuboer, J. F.: Die Funktion des Oddischen Muskels, *Ber. ü. d. ges. Physiol. u. exper. Pharmacol.* 51: 81, 1929.
174. Nuboer, J. F.: Studien über das extrahepatische Gallenwegssystem, *Frankfurt. Ztschr. f. Path.* 41: 198-249, 454-511, 1931.
175. Nygaard, K. K.: On Post-Cholecystectomy Colics, With Report of a Case, *Acta chir. Scandinav.* 81: 309, 1938.
176. Oddi, R.: D'une disposition a sphincter spéciale de l'ouverture du canal cholédoque, *Arch. ital. de biol.* 8: 317, 1887.
177. Oddi, R.: Effets de l'extirpation de la vésicule biliaire, *Arch. ital. de biol.* 10: 425, 1888.
178. Oddi, R.: Sulla tonicità dello sfintere del coledoco, *Archiv. per le sc. med.* 12: 333, 1888.
179. Oddi, R., and Rosciani, G. D.: Sulla esistenza di speciali gangli nervosi in prossimità dello sfintere del coledoco, *Monitore zoo. ital.* 5: 216-219, 1894.
180. Oddi, R., and Rosciani, G. D.: Sur l'existence de ganglions nerveux spéciaux en proximité du sphincter du cholédoque, *Arch. ital. de biol.* 23: 459, 1895.
181. Okada, S.: On the Secretion of Bile, *J. Physiol.* 49: 457-482, 1914-1915.
182. Pavel, I.: Ictère par obstacle fonctionnel dû au spasme du sphincter d'Oddi avec examen anatomique, *Presse méd.* 103: 1948-1950, 1932.
183. Pavel, I.: Jaundice Caused by Functional Obstruction. Reflex Spasm of the Sphincter of Oddi, *J. A. M. A.* 110: 566-569, 1938.
184. Pavlov, I. P.: The Work of the Digestive Glands, translation by W. H. Thompson, ed. 2, London, 1910, Charles Griffin & Co.
185. Payne, R. L.: Postoperative Care in Surgery of the Bile Tract, *J. A. M. A.* 109: 1436-1440, 1937.
186. Porsio, A.: Contributo alla struttura della porzione intraparietale del dotto coledoco e del dotto pancreatico dell'uomo, con speciale riguardo allo sfintere di Oddi, *Arch. ital. di anat. e di embriol.* 29: 127-155, 1931.
187. Potter, J. C., and Mann, F. C.: Pressure Changes in the Biliary Tract, *Am. J. M. Sc.* 171: 202, 1926.
188. Pribram, B. O.: New Methods in Gall-Stone Surgery, *Surg., Gynec. & Obst.* 60: 55-64, 1935.
189. Puestow, C. B.: The Discharge of Bile Into the Duodenum: An Experimental Study, *Arch. Surg.* 23: 1013-1029, 1931.
190. Puestow, C. B.: Surgery of the Gall-Bladder and Bile Ducts, *Illinois M. J.* 71: 54-58, 1937.
191. Puestow, C. B.: Changes in Intracholedochal Pressure Following Cholecystectomy, *Surg., Gynec. & Obst.* 67: 82-86, 1938.
192. Puestow, C. B., and Morrison, R. B.: The Relationship of Cholecystitis and Cholecystectomy to Dilatation of the Choledochus, *Ann. Surg.* 101: 599-602, 1935.
193. Reach, F.: Untersuchungen zur Physiologie und Pharmakologie der Gallenwege, *Zentralbl. f. Physiol.* 26: 1318, 1913.
194. Reach, F.: Die Beeinflussung der Gallenwege durch Pharmaka, *Wien. klin. Wchnschr.* 27: 72-74, 1914.
195. Reach, F.: Der Schliessmuskel des Ductus choledochus in funktioneller Beziehung, *Arch. f. exper. Path. u. Pharmacol.* 85: 178-198, 1920.
196. Rehfuess, M. E., and Nelson, G. M.: The Medical Treatment of Gallbladder Disease, Philadelphia, 1935, W. B. Saunders Co.
197. Reich, H.: Choledochal Denervation. A New Procedure for the Relief of Biliary Dyskinesia, *Surg., Gynec. & Obst.* 71: 39-43, 1940.
198. Rost, F.: Die funktionelle Bedeutung der Gallenblase. Experimentelle und anatomische Untersuchungen nach Cholecystektomie, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 26: 710-770, 1913.
199. Sandblom, P., Bergh, G. S., and Ivy, A. C.: Cholecystoduodenostomy Combined With Pyloric Exclusion, *Ann. Surg.* 104: 702-710, 1936.
200. Sandblom, P., Voegtlin, W. L., and Ivy, A. C.: The Effect of Cholecystokinin on the Mechanism (Sphincter of Oddi), *Am. J. Physiol.* 1 . . .
201. Saralegui, J. A.: Roentgen Findings in the Exploration of the Bile Ducts, *Am. J. Roentgenol.* 45: 360-370, 1941.

202. Schmidt, C. R., Beazell, J. M., Atkinson, A. J., and Ivy, A. C.: The Effect of Therapeutic Agents on the Volume and the Constituents of Bile, *Am. J. Digest. Dis.* 5: 613-617, 1938.
203. Schmidt, C. R., Beazell, J. M., Berman, A. L., Ivy, A. C., and Atkinson, A. J.: Studies on the Secretion of Bile, *Am. J. Physiol.* 126: 120-135, 1939.
204. Schmidt, C. R., and Ivy, A. C.: Effect of Cholecystectomy on Extra-Hepatic Ducts in the Rabbit and Guinea Pig. *Proc. Soc. Exper. Biol. & Med.* 36: 89-92, 1937.
205. Schmidt, C. R., and Ivy, A. C.: The General Function of the Gall Bladder. Do Species Lacking a Gall Bladder Possess Its Functional Equivalent? The Bile and Pigment Output of Various Species of Animals, *J. Cell. & Comp. Physiol.* 10: 365-383, 1937.
206. Schmieden, V., and Niessen, H.: Die Erkrankungen der steinfreien extrahepatischen Gallenwege, *Deutsche Ges. f. inn. Med.* 44: 302-354, 1932.
207. Schragar, V. L., and Ivy, A. C.: Symptoms Produced by Distention of the Gallbladder and Biliary Ducts, *Surg., Gynec. & Obst.* 47: 1-13, 1928.
208. Schube, P. G., Myerson, A., and Lambert, R.: The Effect of Benzedrine, Benzedrine and Atropine, and Atropine on the Gall Bladder, *Am. J. M. Sc.* 197: 57-61, 1939.
209. Schwegler, R. A., Jr., and Boyden, E. A.: The Development of the Pars Intestinalis of the Common Bile Duct in the Human Fetus, With Special Reference to the Origin of the Ampulla of Vater and the Sphincter of Oddi. I. The Involution of the Ampulla, *Anat. Rec.* 67: 441-467, 1937.
210. Schwegler, R. A., Jr., and Boyden, E. A.: The Development of the Pars Intestinalis of the Common Bile Duct in the Human Fetus, With Special Reference to the Origin of the Ampulla of Vater and the Sphincter of Oddi. II. The Early Development of the Musculus Proprius, *Anat. Rec.* 68: 17-41, 1937.
211. Schwegler, R. A., Jr., and Boyden, E. A.: The Development of the Pars Intestinalis of the Common Bile Duct in the Human Fetus, With Special Reference to the Origin of the Ampulla of Vater and the Sphincter of Oddi. III. The Composition of the Musculus Proprius, *Anat. Rec.* 68: 193-219, 1937.
212. Shi, K.: The Influence of the Gall-Bladder, Oddi's Muscle and the Duodenum Upon the Outflow of Bile. I. Injection of Visceral Nerve Poisons and Pituitrin, *Jap. J. Gastroenterol.* 5: 19-25, 1933.
213. Shi, K.: The Influence of the Gall-Bladder, Oddi's Muscle and the Duodenum Upon the Outflow of Bile. II. Observations Made After the Injection of Some Substances Into the Duodenum, *Jap. J. Gastroenterol.* 5: 26-30, 1933.
214. Snell, A. M., Kegaries, D. L., and Minty, E. W.: A Clinic on Disease of the Biliary Tract, *Journal-Lancet* 57: 522-526, 1937.
215. Snell, A. M., McGowan, J. M., and Butsch, W. L.: Colics Following Cholecystectomy: the Probable Mechanism of Their Production, *Rhode Island M. J.* 19: 113-119, 1936.
216. Spier, E., Neuwelt, F., and Necheles, H.: Clinical Study of a New Synthetic Spasmolytic Drug: Diphenylacetyl-diethylaminoethanol, *Am. J. Digest. Dis.* 6: 357-359, 1939.
217. Stepp, W.: Ueber die Gewinnung von Gallenblaseninhalten mittels der Duodenalsonde durch Einspritzung von Witte-Peptonlösung ins Duodenum, *Ztschr. f. klin. Med.* 89: 313-344, 1920.
218. Strauss, A. A., Strauss, S. F., Crawford, R. A., and Strauss, H. A.: Chronic Biliary Stasis: Treatment by Choledochoduodenostomy and Gastroenterostomy, *J. A. M. A.* 101: 1365-1370, 1933.
219. Sussman, M. L.: Emptying of the Normal Gallbladder, *Am. J. Roentgenol.* 38: 867-871, 1937.
220. Tanturi, C. A., and Ivy, A. C.: On the Existence of Secretory Nerves in the Vagi for and the Reflex Excitation and Inhibition of Bile Secretion, *Am. J. Physiol.* 121: 270-283, 1938.
221. Thiessen, N. W.: The Anatomy of the Sphincter of Oddi, *Am. J. Surg.* 53: 94-101, 1941.
222. Treplin: Zur Aetiologie und Therapie der Pseudorecivide nach Gallensteinoperationen, *Beitr. z. klin. Chir.* 126: 103-112, 1922.
223. Vesalius, A.: *De humani corporis fabrica libri septum* (1543), cited by Boyden.<sup>25</sup>
224. Voegtlin, W. L., and Ivy, A. C.: An Investigation Concerning Certain Substances Reported to Affect the Motility of the Gall Bladder, *Am. J. Digest. Dis.* 1: 174-177, 1934.

171. Newcomer, N. B., and Newcomer, E.: Further Discussion of the Relations of the Antrum and Cap to the Gall Bladder as Factors in Emptying the Gall Bladder, *Radiol.* 25: 547-565, 1935.
172. Newman, C.: Physiology of the Gall-Bladder and Its Functional Abnormalities, *Lancet* 1: 785-791, 1933.
173. Nuboer, J. F.: Die Funktion des Oddischen Muskels, *Ber. ü. d. ges. Physiol. u. exper. Pharmacol.* 51: 81, 1929.
174. Nuboer, J. F.: Studien über das extrahepatische Gallenwegssystem, *Frankfurt. Ztschr. f. Path.* 41: 193-249, 454-511, 1931.
175. Nygaard, K. K.: On Post-Cholecystectomy Colics, With Report of a Case, *Acta chir. Scandinav.* 81: 309, 1938.
176. Oddi, R.: D'une disposition a sphincter spéciale de l'ouverture du canal cholédoque, *Arch. ital. de biol.* 8: 317, 1887.
177. Oddi, R.: Effets de l'extirpation de la vésicule biliaire, *Arch. ital. de biol.* 10: 425, 1888.
178. Oddi, R.: Sulla tonicita dello sfintere del coledoco, *Archiv. per le sc. med.* 12: 333, 1888.
179. Oddi, R., and Rosciano, G. D.: Sulla esistenza di speciali gangli nervosi in prossimita dello sfintere del coledoco, *Monitore zoo. ital.* 5: 216-219, 1894.
180. Oddi, R., and Rosciano, G. D.: Sur l'existence de ganglions nerveux spéciaux en proximité du sphincter du cholédoque, *Arch. ital. de biol.* 23: 459, 1895.
181. Okada, S.: On the Secretion of Bile, *J. Physiol.* 49: 457-482, 1914-1915.
182. Pavel, I.: Ictère par obstacle fonctionnel dû au spasme du sphincter d'Oddi avec examen anatomique, *Presse méd.* 103: 1948-1950, 1932.
183. Pavel, I.: Jaundice Caused by Functional Obstruction. Reflex Spasm of the Sphincter of Oddi, *J. A. M. A.* 110: 566-569, 1938.
184. Pavlov, I. P.: The Work of the Digestive Glands, translation by W. H. Thompson, ed. 2, London, 1910, Charles Griffin & Co.
185. Payne, R. L.: Postoperative Care in Surgery of the Bile Tract, *J. A. M. A.* 109: 1436-1440, 1937.
186. Porsio, A.: Contributo alla struttura della porzione intraparietale del dotto coledoco e del dotto pancreatico dell'uomo, con speciale riguardo allo sfintere di Oddi, *Arch. ital. di anat. e di embriol.* 29: 127-155, 1931.
187. Potter, J. C., and Mann, F. C.: Pressure Changes in the Biliary Tract, *Am. J. M. Sc.* 171: 202, 1926.
188. Pribram, B. O.: New Methods in Gall-Stone Surgery, *Surg., Gynec. & Obst.* 60: 55-64, 1935.
189. Puestow, C. B.: The Discharge of Bile Into the Duodenum: An Experimental Study, *Arch. Surg.* 23: 1013-1029, 1931.
190. Puestow, C. B.: Surgery of the Gall-Bladder and Bile Ducts, *Illinois M. J.* 71: 54-58, 1937.
191. Puestow, C. B.: Changes in Intracholedochal Pressure Following Cholecystectomy, *Surg., Gynec. & Obst.* 67: 82-86, 1938.
192. Puestow, C. B., and Morrison, R. B.: The Relationship of Cholecystitis and Cholecystectomy to Dilatation of the Choledochus, *Ann. Surg.* 101: 599-602, 1935.
193. Reach, F.: Untersuchungen zur Physiologie und Pharmakologie der Gallenwege, *Zentralbl. f. Physiol.* 26: 1318, 1913.
194. Reach, F.: Die Beeinflussung der Gallenwege durch Pharmaka, *Wien. klin. Wchnschr.* 27: 72-74, 1914.
195. Reach, F.: Der Schliessmuskel des Ductus choledochus in funktioneller Beziehung, *Arch. f. exper. Path. u. Pharmacol.* 85: 178-198, 1920.
196. Rehfuess, M. E., and Nelson, G. M.: The Medical Treatment of Gallbladder Disease, Philadelphia, 1935, W. B. Saunders Co.
197. Reich, H.: Choledochal Denervation. A New Procedure for the Relief of Biliary Dyskinesia, *Surg., Gynec. & Obst.* 71: 39-43, 1940.
198. Rost, F.: Die funktionelle Bedeutung der Gallenblase. Experimentelle und anatomische Untersuchungen nach Cholecystektomie, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 26: 710-770, 1913.
199. Sandblom, P., Bergh, G. S., and Ivy, A. C.: Cholecystoduodenostomy Combined With Pyloric Exclusion, *Ann. Surg.* 104: 702-710, 1936.
200. Sandblom, P., Voegtlin, W. L., and Ivy, A. C.: The Effect of Cholecystokinin on the Choledochoduodenal Mechanism (Sphincter of Oddi), *Am. J. Physiol.* 113: 175-180, 1935.
201. Saralegui, J. A.: Roentgen Findings in the Exploration of the Bile Ducts, *Am. J. Roentgenol.* 45: 360-370, 1941.

## Book Reviews

---

**Macleod's Physiology in Modern Medicine.** Edited by Philip Bard. Ed. 9. Pp. 1256, with 387 illustrations. St. Louis, 1941, The C. V. Mosby Co. \$10.

The first edition of *Macleod's Physiology* appeared in 1918 and was immediately recognized as an important contribution in this field of endeavor. The fact that it is now going into its ninth edition is sufficient evidence of its establishment as a distinguished and authoritative text.

The arrangement of the present edition is similar to that of the eighth edition which "was largely rewritten by a group of authors each of whom contributed a section devoted to one of the major fields of physiology." Besides the authors who contributed to the previous edition there have been added in the present edition, Howard J. Curtis who has rewritten the chapters on electrical excitation and conduction of the nerve impulses and Walter S. Root who has contributed a chapter on the urinary bladder. The extensive scope of the book is indicated by the bibliography which covers sixty six pages. These references are placed at the end of the volume and are conveniently arranged according to the major section and portion of the text covered. This textbook, which has been brought up to date, not only fulfills its original purpose of serving "as a guide to the clinical application of physiology and biochemistry," but continues to be an invaluable, ready, and reliable reference to clinicians interested in experimental investigations.

---

**The Intervertebral Disc: With Special Reference to Rupture of the Annulus Fibrosus With Herniation of the Nucleus Pulposus.** By F. Keith Bradford and R. Glen Spurling. Ed 1. Pp 158, with 45 illustrations. Springfield, Ill., Charles C Thomas, Publisher. \$4.

*The Intervertebral Disc*, a valuable 150 page monograph, is dedicated to Dr. W. Jason Mixer, Dr. Joseph S. Barr, and Dr. Aubrey O. Hampton, the neurosurgeon, orthopedist, and radiologist whose contributions to the knowledge of intervertebral disc lesions have done so much in placing the surgical treatment of this common and incapacitating condition on a practical basis. The book gives an excellent description of the development and anatomy of these structures, as well as of the physiologic and pathologic conditions which may lead to rupture of the annulus fibrosus and herniation of the nucleus pulposus.

The authors' concept of the innervation of the discs and the posterior longitudinal ligament is of special interest, because it accounts for the diffuse lumbar backache which is often present in addition to the sharp sciatic pain. So also is their evidence that a differential diagnosis can be made between a protrusion of the disc at the fourth and one at the fifth lumbar interspace by careful neurologic examination. In typical cases this is of great value and sometimes obviates the need for contrast myelography. Besides containing a clearly drawn picture of the clinical and radiologic findings in the common syndrome of herniation of the two lowest lumbar discs, the rarer instances of protrusion in the cervical and other regions are not neglected. It is unfortunate that the manuscript should have been sent to the printers too early for the authors to have had experience with Kubik and Hampton's

225. Volini, I. F., and O'Brien, G. F.: The Treatment of Biliary Colic, *M. Clin. North America* 23: 75-82, 1939.
226. Walters, W.: The Pain-Mechanism in Biliary Disease, *Surg., Gynec. & Obst.* 63: 251-252, 1936.
227. Walters, W.: The Pathological Physiology of Stone in the Common Bile Duct, *Surg., Gynec. & Obst.* 63: 417-424, 1936.
228. Walters, W.: Abnormal Function of the Common Bile Duct Resulting From Benign Conditions, *Ann. Surg.* 106: 726-736, 1937.
229. Walters, W.: Lesions of the Extrahepatic Biliary Tract, *J. A. M. A.* 111: 2477-2482, 1938.
230. Walters, W.: Personal Experiences in the Treatment of Benign Obstructing Lesions of the Biliary Tract, *SURGERY* 3: 884-892, 1938.
231. Walters, W.: Recent Advances in the Surgical Treatment of Lesions of the Biliary Tract, *SURGERY* 3: 786-798, 1938.
232. Walters, W., and Gray, H. K.: Progress in Surgery of the Biliary Tract With a Report of Surgical Procedures on the Pancreas for 1935, *Proc. Staff Meet., Mayo Clin.* 11: 729-734, 1936.
233. Walters, W., McGowan, J. M., Butsch, W. L., and Knepper, P. A.: The Pathologic Physiology of the Common Bile Duct: Its Relation to Biliary Colic, *J. A. M. A.* 109: 1591-1596, 1937.
234. Walters, W., and Snell, A. M.: Diseases of the Gallbladder and Bile Ducts, Philadelphia, 1940, W. B. Saunders Co.
235. Walters, W., and Thiessen, N. W.: Visual Methods of Studying the Physiology of the Common Bile Duct: I. The Problem of Pancreatitis and Sphincteritis, *Proc. Staff Meet., Mayo Clin.* 9: 772-775, 1934.
236. Walters, W., and Wesson, H. R.: Fragmentation and Expulsion of a Common Duct Stone Into the Duodenum by Using Ether and Amyl Nitrite, *Surg., Gynec. & Obst.* 65: 695-697, 1937.
237. Wangenstein, O. H.: Cholangitis Following Cholecystenterostomy, *Ann. Surg.* 87: 54-65, 1928.
238. Weir, J. F., and Snell, A. M.: Symptoms That Persist After Cholecystectomy: Their Nature and Probable Significance, *J. A. M. A.* 105: 1093-1098, 1935.
239. Westphal, K.: Muskelfunktion, Nervensystem und Pathologie der Gallenwege: I, II, and III, *Ztschr. f. klin. Med.* 96: 22-150, 1923.
240. Westphal, K., Gleichmann, F., and Mann, W.: Gallenwegsfunktion und Gallensteinleiden, Berlin, 1931, Julius Springer.
241. Whitaker, L. R.: The Mechanism of the Gallbladder, *Am. J. Physiol.* 78: 411-436, 1926.
242. Whitaker, L. R.: The Mechanism of the Gallbladder and Its Relation to Cholelithiasis, *J. A. M. A.* 88: 1542-1548, 1927.
243. Winkelstein, A.: Some Observations on the Entrance of Bile Into the Duodenum, *Surg., Gynec. & Obst.* 40: 545-547, 1925.
244. Winkelstein, A., and Aschner, P. W.: The Pressure Factors in the Biliary-Duct System of the Dog, *Am. J. M. Sc.* 168: 812-819, 1924.
245. Zander, P.: Zum Thema der Stauungsgallenblase und des Gallenkolikrezidivs, *München. med. Wchnschr.* 70: 1173-1175, 1923.
246. Zollinger, R.: Significance of Pain and Vomiting in Cholelithiasis, *J. A. M. A.* 105: 1647-1652, 1935.
247. Zopf, G.: Gallensteinrezidive. Ursache und Behandlung der Rezidivbeschwerden nach Cholecystektomie, *Chirurg.* 10: 389-396, 1938.
248. Zuekerman, C., Kogut, B., and Jacobi, M.: Studies in Human Biliary Physiology: I. Fasting Rate and Quantity of Bile Secretion, *Am. J. Digest. Dis.* 6: 183-185, 1939.

# SURGERY

VOL. 11

MARCH, 1942

No. 3

## Original Communications

### STUDIES ON THE INTRAVENOUS ADMINISTRATION OF WHOLE BOVINE PLASMA AND SERUM TO MAN\*†

ARNOLD J. KREMEN, M.D., HOWARD HALL, M.D.,  
HERMAN K. KOSCHNITZKE, M.D., BEATRICE STEVENS, B.S., AND  
OWEN H. WANGENSTEEN, M.D., MINNEAPOLIS, MINN.

*(From the Department of Surgery, University of Minnesota Medical School)*

THE search for a satisfactory blood substitute has received a strong stimulus in recent times from its obvious need in military surgery and in civil practice for combating states of contracted blood volume and protein stores.

As indicated by Blalock and Mason,<sup>1</sup> intravenous saline or glucose solutions are of much greater value in prevention than in treatment of shock. The use of pectin,<sup>2</sup> recently reported by Hartman and his co-workers, appears to afford promise for cases of contracted blood volume, but would not supply parenteral protein for nutritional purposes. Sterile human ascitic fluid<sup>3</sup> has been used and apparently can be tolerated, but its supply is obviously limited and its protein content low. The use of acacia,<sup>4</sup> which reached its greatest popularity shortly after the last war, has been shown to produce such undesirable side and delayed effects that in recent years its use has been almost entirely supplanted by whole human blood, serum, or plasma. These, it is generally agreed today, are the most desirable agents for combating surgical shock.

However, the source of human material is limited and its procurement and preparation so expensive as to curtail any broad application. On the other hand, the bovine source of blood from which one might fashion a satisfactory blood substitute is practically unlimited and its usefulness unexplored.

\*The researches presented here were supported by grants of the Graduate School of the University of Minnesota, the Augustus L. Searle Fund for Surgical Research, the Minnesota Medical Foundation and by a grant for technical assistance by the Work Projects Administration, Official Project No. 165-1-71-124, Subproject No. 399.

†Presented Nov. 4, 1941, before the Surgical Forum on Fundamental Surgical Problems in Boston, Mass.

Received for publication, Dec. 15, 1941.



technique for removing intraspinally injected lipiodol, because this maneuver has so effectively overcome the current objections to the use of accurate contrast localization of these lesions. The surgical description of removing the protruded disc through a limited hemilaminectomy incision is given in a most lucid fashion and the results analyzed in a series of 166 cases. Whether to include a spinal fusion or not remains the most debated point in the treatment of these lesions. The authors, who belong to the nonfusion school, have perhaps dismissed this question with too little consideration.

In addition to presenting the authors' experience in a large series of intervertebral disc lesions, the volume contains a valuable review of the formidable literature which has accumulated on this much discussed topic. The book should appeal particularly to neurosurgeons and orthopedists, and should be of special help to newcomers in these fields.

## PROCEDURE AND PREPARATION

With the cooperation of Dr. W. L. Boyd, of the department of veterinary medicine, four cows free of tuberculosis and brucellosis were placed at our disposal. Four to 5 liters of blood were obtained from each cow every two weeks. Blood was drawn from the jugular vein using a sterile paracentesis trocar and collected into sterile, 4 liter Erlenmeyer flasks. Latterly, through the generosity of Mr. R. A. Keyer, of the Armour Packing Company of South Saint Paul, Minn., a larger stock was placed at our disposal. At the packing house, blood is drawn aseptically from the jugular vein with the same apparatus immediately after the animals are stunned by a blow on the head and suspended from the ceiling by the hindlegs. If serum is to be obtained, the blood is allowed to clot in the collecting flask, and after twenty-four and forty-eight hours the serum is decanted off from a special outlet at the bottom of the flask into 250 c.c. centrifuge tubes and centrifuged for one-half hour at 2,500 r.p.m. If plasma is to be obtained, sufficient sodium citrate solution is added to make a final concentration of 0.3 per cent, the red blood cells being removed by centrifugation. Sulfanilamide in final concentration of 20 mg. per cent was used as a preservative.

Although the entire process was done aseptically, sera were passed through a Seitz filter using E.K. pads, size 14, then bottled and sealed without exposure to the atmosphere. Cultures on veal infusion and brain broth were sterile five to seven days before the material was used. Difficulty was encountered in filtering plasma through the Seitz filter, while serum passed through readily. In addition, plasma, after standing, precipitates fibrin which must be filtered off before using the material. Frozen plasma was prepared by placing the bottles in the freezing coils of a refrigerator for twenty-four hours and then storing them in the frozen state until used. If left out at room temperature, it melts in about one hour. A flaky precipitate of fibrin remains, which was removed before using by filtration through several layers of sterile gauze.

## MODIFICATION OF WHOLE BOVINE PLASMA

In order to eliminate the fibrinogen fraction, serum rather than plasma was used. Subsequently, it was found that whole bovine plasma and serum contain hemolysins and hemagglutinins to human red blood cells of the various blood groups. Partial removal of these by adsorption on human red blood cells is possible and apparently reduced the incidence of reactions.

In adsorbing the bovine serum, fresh human cells doubly washed with normal saline solution are mixed gently with the bovine serum in a ratio of 1:5 by volume, and removed in thirty minutes by centrifuga-

Animals have been used principally for immune sera of many sorts, employing the horse as the principal donor. Why the bovine family has never been used widely is not clear, but apparently the principal reason is its natural immunity to most infectious diseases. In addition, for technical reasons, the horse is easier to bleed, it can be trained to cooperate, and it is easier to care for and to keep clean. However, these are not valid contraindications for neglecting such a cheap and ready source of blood proteins, which, to date, has never been given a thorough experimental or clinical exploration.

Most immunologists have regarded bovine serum as antigenic and unsafe for intravenous injection into man. When plans for this study were being scrutinized a number of years ago, the chief deterrent to undertaking the investigation was the prevalent impression among immunologists that bovine serum was even more antigenic and less compatible to man than was horse serum. The paucity of factual data on the matter was striking. As related above, it was our inference that the horse rather than the bovine was selected for the preparation of immune sera because of the natural immunity of the bovine to the common pyogenic organisms. We were unable to find factual data supporting the alleged toxicity of bovine plasma. We did find that Shortell, Cotting, and Leary<sup>5</sup> (1916) reported the use of bovine plasma principally in treatment of wounds. Penna and associates<sup>6</sup> reported the successful intravenous and intramuscular use of normal bovine serum in treatment of anthrax.

In previous publications<sup>7, 8</sup> we have reported some of our results with bovine plasma; namely, that it can be given in fairly large amounts to some people and that it is apparently retained by the body. On the basis of skin tests with the various fractions of whole bovine plasma, it appeared that the albumin fraction was the least reactive. Recently Colm and his associates<sup>9, 10</sup> have succeeded in fractionating whole bovine plasma into its various constituents by fractional precipitation at  $-5^{\circ}$  C. with ethyl alcohol. Purified albumin so obtained is now under clinical trial and preliminary studies seem most encouraging. In a letter to the *Journal of the American Medical Association*, Keys, Taylor, and Savage<sup>11</sup> have outlined their experience with fractionation of animal plasma proteins and feel also that a satisfactory human blood substitute may be fashioned from animal blood. However, since the problem of fractionation of plasma proteins is chiefly a chemical one requiring the background, equipment, and facilities of a well-established physical chemistry laboratory rather than a surgical laboratory, we have confined our efforts to studies of: (1) an evaluation of the usefulness of whole bovine plasma and serum in man, (2) a study of the items contributing to reactions with the use of whole bovine plasma or serum, and (3) the effect on nitrogen balance, of bovine and human plasma proteins administered intravenously to man.

intravenously; next day 5 c.e. diluted to 10 c.e. was given, and somewhat later, 50 c.e. diluted to 100 c.e. was given. If no reactions occurred, amounts of 250 c.e. diluted with an equal amount of saline or 5 per cent dextrose solution were given. The rate of administration was slow. The preliminary injections of 1 and 10 c.e. were given in about five minutes. The larger injections were given by gravity drip at a rate of 4 to 5 c.e. per minute. If any untoward manifestations appeared, the injection was discontinued immediately.

#### RESULTS OF INJECTION

In Tables II to IX are tabulated the results of injection of whole bovine plasma, serum, and adsorbed serum to 120 patients. The reactions of all are summarized in Table X. Patients who did not exhibit untoward immediate symptoms received total amounts of from 300 to 2,500 c.e. in divided doses. Under immediate reactions are included all untoward manifestations the day of injection. About 50 per cent of reactions are febrile in character, usually initiated by a chill one-half to one hour after the start of the injection. Other reactions, such as immediate urticaria, edema of eyelids, flushing of skin, backache, gastrointestinal upsets with diarrhea and/or vomiting, dizziness, and severe anaphylactic reactions make up the remainder.

In the whole plasma (Table II) and serum (Table IV) groups, the incidence of immediate reactions was about the same; namely, 58.3 and 66.6 per cent. Freezing of plasma during storage, as recommended by Strumia and McGraw,<sup>12</sup> does not appear to alter the reactive properties of bovine plasma (Table III) for the incidence of reactions was the same as in the other groups. By employing the technique of adsorbing bovine serum on human red blood cells, the incidence of reactions was materially reduced; namely, to 24.5 per cent in 53 patients. In general, the incidence of reactions was fairly constant regardless of the group of red blood cells used for adsorption. Also, there does not appear to be any correlation between the blood group of recipient and the red blood cell group used for adsorption. From these data, it appears likely that, whatever is adsorbed by the red blood cells is either species specific or nonspecific rather than blood group specific. In order to explore this possibility, kaolin was used as the adsorbing medium. In Table I it will be noted that this does not remove any of the hemolysins or hemagglutinins. Five reactions in 13 patients were observed, an incidence of 38.5 per cent, indicating a result midway between serum adsorbed on various groups of red blood cells and whole untreated serum.

In Tables II to IX, the heading "Total Amount Given" represents the summation of all the material injected, while the heading "Amount Causing Reaction" is the single dose at the time at which reaction

tion. If this time is exceeded, hemolysis occurs usually. Apparently, union of reacting antibodies occurs before hemolysis becomes evident, and if the red blood cells are removed by centrifugation at this time, clear unhemolyzed serum can be obtained, with most of the hemolysins and about 50 per cent of the hemagglutinins removed, as indicated in Table I. For these studies serial dilution of serum with normal saline

TABLE I

TITER OF HEMOLYSINS AND HEMAGGLUTININS IN BOVINE SERUM AND PLASMA TO HUMAN RED BLOOD CELLS BEFORE AND AFTER ADSORPTION WITH HUMAN RED BLOOD CELLS AND KAOLIN

BOVINE PLASMA OR SERUM	BEFORE ADSORPTION WITH HUMAN RED BLOOD CELLS		AFTER ADSORPTION WITH HUMAN RED BLOOD CELLS	
	TITER OF HEMOLYSIN	TITER OF AGGLUTININ	TITER OF HEMOLYSIN	TITER OF AGGLUTININ
Serum 15	1:10	1:20	1:2	1:10
Plasma 15	1:2	1:20	0	1:10
Serum 16	1:10	1:25	1:5	1:20
Plasma 16	0	1:25	0	1:25
Serum 17	1:10	1:25	1:3½	1:25
Plasma 6	1:5	1:25	0	1:10
Serum 7	1:3½	1:10	1:2	1:5
	BEFORE ADSORPTION WITH KAOLIN		AFTER ADSORPTION WITH KAOLIN	
Serum 86	1:2½	1:3½	1:2	1:5
Serum 95	1:3½	1:5	1:3½	1:10
Serum 96	1:3½	1:10	1:2½	1:5
Serum 97	1:5	1:20	1:5	1:20
Serum 98	1:5	1:20	1:5	1:20

solution and 1 per cent suspension of human red blood cells were used and read macroscopically after one hour of incubation at 37° C. In order to explore the possibility of this adsorption's being specific for the erythrocytes, kaolin was used as the adsorbing medium. As noted in Table I, it failed to decrease the titer of either hemolysins or hemagglutinins. Although the entire adsorption procedure was done aseptically, all adsorbed serum was passed through the Seitz filter and cultured as described above before using.

#### SELECTION OF PATIENTS AND TECHNIQUE OF INJECTION

Patients selected for trial on bovine plasma and serum have been restricted largely to those with carcinoma, usually inoperable. A preliminary skin test was done on all patients using 0.1 c.c. of 1:10 dilution of serum with normal saline solution. In the main, the only patients to whom we attempted to administer bovine plasma or serum were those in whom only slight or negative skin reactions were manifest. Our preliminary experience indicated that subjects with marked positive skin wheals,<sup>8</sup> do not take bovine serum well. Following the skin test, 0.1 c.c. of bovine serum diluted to 1 c.c. with normal saline solution is given intravenously. Several hours later, if no reaction occurred, 1 c.c. diluted to 10 c.c. with normal saline solution was given

12. Mr. W. C. (U. H. 679451)	56	Carcinoma of penis	A	1+	650	None	--	None
13. Mr. J. K. (U. H. 612060)	65	Lung abscess	A	0	300	None	--	None
14. Mr. H. L. (U. H. 686526)	61	Carcinoma of pancreas	AB	0	175	Chill; temperature, 101°	150	None
15. Mr. W. M. (U. H. 691429)	66	Carcinoma of mouth		0	155	Chill; temperature, 104.6°	50	General urticaria in 2 days
16. Mr. C. H. (U. H. 691306)	61	Carcinoma of stomach	AB	0	556	Flush of skin	5	General urticaria in 4 days
17. Mr. G. S. (U. H. 691203)	10	Carcinoma of stomach	A	0	556	None	--	None
18. Mr. F. G. (U. H. 691278)	68	Common duct stone	O	0	306	General urticaria	250	General urticaria in 7 days
19. Mrs. H. V. (U. H. 681105)	60	Meleney ulcer		0	206	Pain in chest, backache	150	General urticaria in 6 days
20. Mr. J. N. (U. H. 627438)	62	Hemangioma-thelioma of spine	A	2+	180	Pain in chest, dyspnea	150	General urticaria in 5 days
21. Mr. H. F. (U. H. 695282)	46	Carcinoma of colon		1+	180	Flush, dyspnea, pain in chest	150	General urticaria in 3 days
22. Mr. H. H. (U. H. 695001)	38	Cord tumor	O	1+	556	None	--	General urticaria in 3 days
23. Mr. F. T. (U. H. 691128)	25	Osteogenic sarcoma	A	1+	106	Chill, backache	50	General urticaria in 5 days
24. Mr. J. R. (U. H. 683375)	71	Carcinoma of rectum, asthma	A	1+	2	Anaphylactic response	2	None

TABLE II  
REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF WHOLE BOVINE PLASMA

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mr. W. M. (U. H. 681255)	60	Carcinoma of stomach	B	0	900	Flush, dyspnea	200	Urticaria in 4 days
2. Mr. H. S. (U. H. 681983)	68	Carcinoma of stomach	A	0	1,000	None	--	None
3. Mr. A. T. (U. H. 650019)	70	Carcinoma of stomach	A	0	500	None	--	None
4. Mr. P. L. (U. H. 693894)	68	Carcinoma of stomach	A	0	440	None	--	None
5. Mr. P. C. (U. H. 684487)	64	Carcinoma of stomach	A	0	245	None	--	None
6. Mr. T. S. (U. H. 641802)	37	Bleeding ulcer	O	0	850	None	--	None
7. Mr. H. W. (U. H. 684341)	68	Carcinoma of esophagus	O	0	1,500	None	--	Urticaria in 2 days
8. Mr. B. L. (U. H. 688427)	42	Carcinoma of colon	O	0	1,125	Chill	200	None
9. Mr. H. L. (U. H. 666961)	56	Carcinoma of stomach	A	1+	510	Diarrhea; chill; temperature, 103°	250	None
10. Mr. M. K. (U. H. 683236)	78	Carcinoma of lip	B	0	510	Chill; temperature to 105°	250	None
11. Mr. W. W. (U. H. 683078)	72	Carcinoma of neck	A	1+	110	Chill; temperature, 105°	100	None

TABLE IV  
REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF WHOLE BOVINE SERUM

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mr. B. H. (U. H. 697067)	70	Papilloma of mouth	O	1+	176	Backache	125	Urticaria
2. Mr. M. B. (U. H. 700837)	69	Fractures	A	2+	56	Chill; temperature, 101°	50	
3. Mr. J. D. (U. H. 699116)	56	Carcinoma of rectum	A	0	231	Flush, chilly	225	Urticaria in 7 days
4. Mrs. E. B. (U. H. 700745)	68	Carcinoma of rectum	A	1+	306	Nausea; chill; temperature, 101°	250	
5. Mr. W. S. (U. H. 700406)	60	Carcinoma of rectum	A	0	361	None	--	None
6. Mr. N. P. (U. H. 699634)	68	Carcinoma of neck	A	1+	306	None	--	Urticaria
7. Mrs. M. A. (U. H. 694967)	71	Carcinoma of breast	B	1+	306	None	--	None
8. Mr. J. M. (U. H. 697807)	65	Cholecholethiasis		2+	306	Chill; slight temperature, 100°	250	Urticaria
9. Mr. O. F. (U. H. 670645)	40	Brain tumor		1+	356	None	--	
10. Mr. E. B. (U. H. 600864)	61	Hemangioma	O	1+	56	Urticaria, vomiting, diarrhea	50	
11. Mr. P. Mc. (U. H. 661242)	50	Carcinoma of mouth	A	2+	56	Urticaria	50	
12. Mr. E. R. (U. H. 697238)	67	Lipoma	O	0	0.1	Anaphylactic response	0.1	
13. Mr. D. E. (U. H. 647331)	27	Osteomyelitis	AB	4+	1.1	Severe pain at site of osteomyelitis in spine	1.0	
14. Mrs. S. M. (U. H. 609973)	74	Osteoma	A	1+	300	None	--	
15. Mr. W. C. (U. H. 699745)	64	Carcinoma of rectum	B	0	56	Vomiting, vertigo, nausea	50	



TABLE III  
REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF FROZEN WHOLE BOVINE PLASMA

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mr. F. J. (U. H. 690458)	63	Carcinoma of esophagus	A	Negative	511	Feeling of constriction in chest	200	None
2. Mr. J. H. (U. H. 691907)	56	Carcinoma of esophagus		Negative	556	None	--	None
3. Mr. R. J. (U. H. 691488)	18	Brain tumor	O	Negative	638	Temperature rise, 100 to 102.6°	250	Urticaria in 6 days
4. Mrs. E. M. (U. H. 695037)	43	Carcinoma of breast	AB	2+	556	None	--	None
5. Mr. A. B. (U. H. 691541)	63	Carcinoma of stomach		2+	556	None	--	None
6. Mr. H. H. (U. H. 693852)	63	Carcinoma of stomach	O	Negative	556	None	--	Urticaria in 5 days
7. Mrs. C. H. (U. H. 683532)	61	Carcinoma of rectum	A	Negative	556	None	--	
8. Mrs. P. M. (U. H. 695428)	53	Carcinoma of breast		1+	306	Chill, dyspnea	250	General urticaria in 6 days
9. Miss G. G. (U. H. 695186)	6	Nephrosis	A	2+	76	Dyspnea, asthmatic respiration	40	None
10. Mr. C. D. (U. H. 681384)	76	Carcinoma of mouth	A	Negative	166	Chill, temperature to 101°	150	
11. Mr. L. S. (U. H. 691211)	67	Carcinoma of rectum	O	1+	556	Chill, nausea, headache	250	General urticaria in 4 days
12. Mrs. A. W. (U. H. 650014)	50	Carcinoma of breast	O	Negative	556	None	--	None
13. Mrs. J. E. (U. H. 595736)		Carcinoma of breast	AB	Negative	41	Dyspnea, asthmatic respiration	35	
14. Mr. H. W. (U. H. 681191)	36	Brain tumor	A	1+	56	Temperature to 103°, nausea, vomiting	50	None
15. Mrs. A. M. (U. H. 695651)	54	Carcinoma of breast	A	1+	56	Chill, temperature to 104°	50	

TABLE VI  
REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF GROUP A ADSORBED BOVINE SERUM

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mrs. E. W. (U. II. 698867)	37	Carcinoma of colon	A	1+	612	Severe backache	1	
2. Mrs. H. S. (U. II. 698051)	51	Duodenal ulcer	A	1+	306	Chill	250	Severe urticaria in 4 days
3. Mr. A. S. (U. II. 698210)	60	Carcinoma of stomach	A	0	306	None	--	Urticaria in 6 days
4. Mr. J. C. (U. II. 698866)	76	Carcinoma of stomach	O	0	306	None	--	None
5. Mr. C. S. (U. II. 698650)	62	Carcinoma of stomach	O	0	306	None	--	Urticaria in 10 days
6. Mr. B. K. (U. II. 698076)	55	Osteomyelitis diaphyses	O	0	306	None	--	None
7. Mr. J. L. (U. II. 697511)	62	Leukemia	A	1+	306	None	--	None
8. Mr. A. P. (U. II. 628276)	61	Carcinoma of cheek	O	1+	306	None	--	None
9. Mr. C. S. (U. II. 698996)	62	Carcinoma of colon	B	1+	306	None	--	None
10. Mrs. A. C. (U. II. 698769)	52	Carcinoma of colon	A	0	306	None	--	Urticaria in 6 days
11. Mrs. E. N. (U. II. 631060)	55	Carcinoma of stomach	O	1+	230	Backache	50	Urticaria
12. Mr. C. S. (U. II. 691517)	54	Carcinoma of stomach	AB	1+	2,400 in 6 days	Pulmonary edema (?); temperature, 101°	300	Urticaria in 3 days
13. Mr. A. W. (U. II. 696335)	51	Carcinoma of stomach	O	1+	56	None	--	None
14. Mrs. J. S. (U. II. 700142)	35	Malignant melanoma	AB	1+	306	None	--	Urticaria in 3 days
15. Mr. H. S. (U. II. 699124)	66	Carcinoma of colon	A	1+	500	None	--	None
16. Mr. W. M. (U. II. 700155)	56	Carcinoma of stomach	A	3+	130	Urticaria, dizziness	50	None



TABLE VIII  
REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF GROUP O ADSORBED BOVINE SERUM

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mrs. A. R. (U. II. 700102)	61	Carcinoma of breast	A	0	306	None	--	None
2. Mr. F. F. (U. II. 700100)	47	Carcinoma of colon	O	0	356	None	--	Urticaria in 7 days
3. Mr. M. D. (U. II. 695457)	62	Carcinoma of rectum	O	1+	56	Temperature, 103°; urticaria; chill	50	Urticaria
4. Mrs. S. L. (U. II. 700728)	61	Carcinoma of rectum	A	0	306	None	--	Urticaria in 7 days
5. Mr. J. M. (U. II. 700143)	55	Carcinoma of colon	O	0	306	None	--	None
6. Mr. R. P. (U. II. 696248)	62	Carcinoma of mouth	A	0	306	None	--	None
7. Mr. N. M. (U. II. 702113)	72	Carcinoma of face	A	0	306	None	--	Urticaria in 4 days
8. Mr. T. C. (U. II. 700746)	35	Tuberculosis		1+	306	None	--	Urticaria in 4 days
9. Mrs. A. D. (U. II. 691666)	52	Osteomyelitis	A	0	306	None	--	None
10. Mrs. C. H. (U. II. 699318)	40	Carcinoma of stomach	A	1+	306	None	--	None
11. Mrs. M. L. (U. II. 691725)	59	Diverticulosis of colon	O	0	306	None	--	None
12. Mr. R. A. (U. II. 703923)	27	Actinomycosis		0	106	Urticaria, diarrhea	50	

TABLE VII  
REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF GROUP B ADSORBED BOVINE SERUM

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (c.c.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (c.c.)	DELAYED REACTION
1. Mr. W. S. (U. H. 638190)	61	Carcinoma of neck	B	1+	306	None	--	None
2. Mr. A. J. (U. H. 681304)	56	Hypernephroma	A	1+	306	None	--	None
3. Mr. G. E. (U. H. 699770)	58	Carcinoma of colon	A	1+	306	None	--	None
4. Mr. E. B. (U. H. 662052)	55	Carcinoma of tongue	O	0	306	None	--	Urticaria in 6 days
5. Mr. W. T. (U. H. 699726)	62	Fracture	O	2+	306	Chill; temperature, 103°	--	None
6. Mr. W. C. (U. H. 699715)	55	Carcinoma of rectum	O	0	306	None	--	Urticaria in 5 days
7. Mr. R. L. (U. H. 698333)	56	Carcinoma of hand	A	0	306	None	--	
8. Mr. J. K. (U. H. 618854)	80	Carcinoma of prostate	A	1+	306	Urticaria	250	
9. Mrs. A. L. (U. H. 686334)	55	Carcinoma of breast	O	0	361	None	--	Urticaria in 6 days
10. Mr. E. R. (U. H. 699902)	65	Carcinoma of lip	O	0	306	None	--	None
11. Mr. O. H. (U. H. 702708)	55	Carcinoma of stomach	A	2+	306	None	--	None

occurred. It will be noted that the severe, anaphylactic reactions occurred with the smallest doses of material. If a patient tolerates the small initial doses, there is probably no great natural sensitivity. Reactions occurring with the larger doses of bovine plasma were chills, fever, immediate urticaria, flushing of skin, backache, gastrointestinal upsets, and edema of eyelids. In the entire series, three severe anaphylactic reactions occurred (Mr. J. B., Case 24, Table II; Mr. E. R., Case 12, Table V; Mrs. E. C., Case 1, Table V). All exhibited severe collapse with 2 c.c., 0.1 c.c., and 0.1 c.c. respectively. Their skin tests gave no indication of this sensitivity, although Mr. J. B. did give a history of asthma in the past. In all there were marked circulatory collapse, extreme dyspnea, and unconsciousness coming on almost immediately after the injection. All responded to prompt intravenous injection of 0.5 to 1 c.c. of epinephrine, and after fifteen to thirty minutes were back to a fairly normal status. There did not appear to be any sequelae to these reactions. Aside from these three severe reactions, the remainder have been mild to moderate in nature and have not caused us any undue concern. Occasionally amyl nitrite, if given early, was effective in alleviating chills. Histaminase tablets, given by mouth (two tablets t.i.d.) before injections were started, and continued for seven days after injections, did not appear to influence the incidence of either immediate or delayed reactions.

TABLE X  
SUMMARY OF REACTIONS WITH BOVINE SERUM AND PLASMA

	IMMEDIATE REACTIONS			DELAYED REACTIONS*		
	NO. OF PATIENTS	NO.	%	NO. OF PATIENTS	NO. OF REACTIONS	%
Whole bovine plasma	24	14	58.3	19	9	47.3
Frozen bovine plasma	15	9	60.0	10	4	40.0
Whole bovine serum	15	10	66.6	6	4	66.6
Human R.B.C. adsorbed serum						
Group AB	14	4	28.5	10	6	60.0
Group A	16	5	31.3	12	7	58.3
Group B	11	2	18.2	7	3	42.9
Group O	12	2	16.6	9	5	55.5
Total	53	13	24.5	38	21	55.3
Kaolin adsorbed serum	13	5	38.5	8	4	50.0

\*Not all patients were available to determine that delayed reactions occurred. These figures include only those patients on whom we have definite information.

Delayed reactions characterized by generalized urticaria, edema, and gastroenteritis have occurred in about 60 per cent of patients followed. In general, the incidence was the same in all groups. They usually appeared three to ten days after the final injection and lasted forty-eight to seventy-two hours. Although they were quite distressing to the patients, all recovered within three days. Adrenalin in peanut oil proved to be

TABLE IX  
REACTIONS ATTENDING INTRAVENOUS ADMINISTRATION OF KAOLIN ADSORBED BOVINE SERUM

PATIENT	AGE	DIAGNOSIS	BLOOD GROUP	SKIN TEST	TOTAL AMOUNT GIVEN (C.C.)	IMMEDIATE REACTION	AMOUNT CAUSING REACTION (C.C.)	DELAYED REACTION
1. Mr. J. P. (U. H. 705302)	74	Carcinoma of tongue	A	0	46	Chill, temperature to 104°	40	
2. Mr. J. L. (U. H. 705875)	51	Carcinoma of stomach	A	0	56	General urticaria	50	
3. Mr. W. H. (U. H. 705875)	57	Carcinoma of mouth		0	236	Edema of eyelids, gastrointestinal cramps	200	Urticaria in 5 days
4. Mrs. H. G. (U. H. 705359)	71	Carcinoma of rectum	A	0	305	None	--	None
5. Mrs. P. E. (U. H. 702776)	61	Carcinoma of breast	A	1+	306	None	--	
6. Mr. C. L. (U. H. 702930)	60	Diabetic gangrene leg	B	0	56	Nausea, vomiting, vertigo	50	
7. Mr. N. D. (U. H. 703096)	52	Hypernephroma	O	0	131	None	--	
8. Mrs. E. W. (U. H. 703730)	69	Carcinoma of rectum	O	0	56	Temperature to 103°	50	Urticaria
9. Mrs. G. L. (U. H. 705456)	62	Perineal ulcer		0	306	None	--	
10. Mr. M. M. (U. H. 684186)	62	Carcinoma of pancreas		0	306	None	--	None
11. Mr. S. K. (U. H. 702881)	60	Carcinoma of rectum	A	0	306	None	--	Urticaria in 10 days
12. Mrs. L. G. (U. H. 705180)	65	Carcinoma of groin	A	1+	306	None	--	Urticaria
13. Mrs. L. N. (U. H. 702832)	56	Retroperitoneal sarcoma	A	2+	306	None	--	None

occurred. It will be noted that the severe, anaphylactic reactions occurred with the smallest doses of material. If a patient tolerates the small initial doses, there is probably no great natural sensitivity. Reactions occurring with the larger doses of bovine plasma were chills, fever, immediate urticaria, flushing of skin, backache, gastrointestinal upsets, and edema of eyelids. In the entire series, three severe anaphylactic reactions occurred (Mr. J. B., Case 24, Table II; Mr. E. R., Case 12, Table V; Mrs. E. C., Case 1, Table V). All exhibited severe collapse with 2 c.c., 0.1 c.c., and 0.1 c.c. respectively. Their skin tests gave no indication of this sensitivity, although Mr. J. B. did give a history of asthma in the past. In all there were marked circulatory collapse, extreme dyspnea, and unconsciousness coming on almost immediately after the injection. All responded to prompt intravenous injection of 0.5 to 1 c.c. of epinephrine, and after fifteen to thirty minutes were back to a fairly normal status. There did not appear to be any sequelae to these reactions. Aside from these three severe reactions, the remainder have been mild to moderate in nature and have not caused us any undue concern. Occasionally amyl nitrite, if given early, was effective in alleviating chills. Histaminase tablets, given by mouth (two tablets t.i.d.) before injections were started, and continued for seven days after injections, did not appear to influence the incidence of either immediate or delayed reactions.

TABLE X

## SUMMARY OF REACTIONS WITH BOVINE SERUM AND PLASMA

	IMMEDIATE REACTIONS			DELAYED REACTIONS*		
	NO. OF PATIENTS	NO.	%	NO. OF PATIENTS	NO. OF REACTIONS	%
Whole bovine plasma	24	14	58.3	19	9	47.3
Frozen bovine plasma	15	9	60.0	10	4	40.0
Whole bovine serum	15	10	66.6	6	4	66.6
Human R.B.C. adsorbed serum						
Group AB	14	4	28.5	10	6	60.0
Group A	16	5	31.3	12	7	58.3
Group B	11	2	18.2	7	3	42.9
Group O	12	2	16.6	9	5	55.5
Total	53	13	24.5	38	21	55.3
Knolin adsorbed serum	13	5	38.5	8	4	50.0

\*Not all patients were available to determine that delayed reactions occurred. These figures include only those patients on whom we have definite information.

Delayed reactions characterized by generalized urticaria, edema, and gastroenteritis have occurred in about 60 per cent of patients followed. In general, the incidence was the same in all groups. They usually appeared three to ten days after the final injection and lasted forty-eight to seventy-two hours. Although they were quite distressing to the patients, all recovered within three days. Adrenalin in peanut oil proved to be



the most efficacious agent in relieving these symptoms. No instances of delayed food sensitivity to beef or milk have been observed.

On two occasions bovine plasma was used in treatment of shock. One patient with a bleeding ulcer, whose blood pressure was 80/40, was given 300 c.c. bovine plasma intravenously over an hour's time. The blood pressure rose to 130/90 where it was maintained for the next two and one-half hours while an additional 400 c.c. was given. The other patient, given 500 c.c. bovine serum, exhibited a blood pressure rise from 90/70 to 110/80.

To two patient, 2,500 c.c. and 2,400 c.c. of bovine serum were given in divided doses over a six-day period. In one on a metabolism study (Table XII), there was no untoward effect at the time of injections; the other (Mr. C. S., Case 12, Table VI) developed signs of pulmonary congestion after the last injection, which may have been on the basis of pulmonary edema from increased blood volume. However, the possibility of capillary damage and increased permeability must be borne in mind.

Six patients were given reinjections of whole bovine plasma or serum after variable intervals (Table XI). In this group there were three anaphylactic types of response with small doses of bovine serum relieved by prompt administration of adrenalin indicating a 50 per cent incidence of anaphylactic sensitization. Similarly, in guinea pigs, whole bovine plasma was found to produce the anaphylactic state consistently.

#### NITROGEN METABOLISM STUDIES

Metabolic studies were made on 3 patients using whole human plasma and on 3 patients using whole bovine plasma or serum. All patients were essentially afebrile. During the period of study, the patients were on a protein-free diet. Tea, orange juice, nectar, and water were allowed by mouth. Enough dextrose solution was given parenterally to maintain a fairly satisfactory caloric intake and to avoid ketosis. Total urinary output was collected, preserved with toluene, and daily determinations of total urinary nitrogen<sup>13, 14</sup> checked by macro- and micro-Kjeldahl methods, nonprotein nitrogen and urea nitrogen<sup>15</sup> were made. At intervals of every two days, blood plasma protein,<sup>13</sup> urea nitrogen,<sup>16</sup> and nonprotein nitrogen<sup>13</sup> levels were determined. The usual procedure was to keep the patient on a preliminary protein starvation regime for four or five days to allow urinary nitrogen to reach a basal level, then to give whole human or bovine plasma intravenously for a five-day period followed by another period of protein starvation.

Table XII illustrates the effect of intravenous administration of bovine serum on nitrogen metabolism. In the basal period, Jan. 3, 1941, through Jan. 8, 1941, this patient did not reach as low a urinary nitrogen excretion as most of our studies have shown. Usually after ade-

TABLE XI  
REACTIONS ATTENDING SUBSEQUENT INJECTIONS OF BOVINE PLASMA OR SERUM

PATIENT	ORIGINAL INJECTION				SUBSEQUENT INJECTION			
	DATE	SKIN TEST	AMOUNT GIVEN (C.C.)	REACTION	DATE	SKIN TEST	AMOUNT GIVEN (C.C.)	REACTION
Mr. D. G. (U. H. 684187)	9/5/39- 9/6/39	Negative	275	None	10/24/39	Negative	25.0	None
Mr. W. M. (U. H. 681253)	7/7/39- 7/10/39	Negative	800	Dyspnea, skin flush	7/18/39	Negative	100.0	None
Mr. J. C. (U. H. 618201)	8/29/39	Negative	25	None	9/5/39	Negative	50.0	None
Mrs. G. L. (U. H. 705456)	2/21/41- 2/23/41	Negative	306	None	4/2/41	2+	3.0	Anaphylactic response with marked dyspnea, pain in chest, vertigo
Mr. P. T. (U. H. 694428)	5/14/40- 5/15/40	1+	400	Chill, temperature to 103°	4/1/41	1+	1.0	Anaphylactic response, dyspnea, vertigo, extreme apprehension
Mr. W. H. (U. H. 705375)	3/8/41- 3/10/41	Negative	256	Edema of eyelids	4/7/41	2+	2.5	Anaphylactic response, dyspnea, pain in chest

the most efficacious agent in relieving these symptoms. No instances of delayed food sensitivity to beef or milk have been observed.

On two occasions bovine plasma was used in treatment of shock. One patient with a bleeding ulcer, whose blood pressure was 80/40, was given 300 c.e. bovine plasma intravenously over an hour's time. The blood pressure rose to 130/90 where it was maintained for the next two and one-half hours while an additional 400 c.e. was given. The other patient, given 500 c.e. bovine serum, exhibited a blood pressure rise from 90/70 to 110/80.

To two patient, 2,500 c.e. and 2,400 c.e. of bovine serum were given in divided doses over a six-day period. In one on a metabolism study (Table XII), there was no untoward effect at the time of injections; the other (Mr. C. S., Case 12, Table VI) developed signs of pulmonary congestion after the last injection, which may have been on the basis of pulmonary edema from increased blood volume. However, the possibility of capillary damage and increased permeability must be borne in mind.

Six patients were given reinjections of whole bovine plasma or serum after variable intervals (Table XI). In this group there were three anaphylactic types of response with small doses of bovine serum relieved by prompt administration of adrenalin indicating a 50 per cent incidence of anaphylactic sensitization. Similarly, in guinea pigs, whole bovine plasma was found to produce the anaphylactic state consistently.

#### NITROGEN METABOLISM STUDIES

Metabolic studies were made on 3 patients using whole human plasma and on 3 patients using whole bovine plasma or serum. All patients were essentially afebrile. During the period of study, the patients were on a protein-free diet. Tea, orange juice, nectar, and water were allowed by mouth. Enough dextrose solution was given parenterally to maintain a fairly satisfactory caloric intake and to avoid ketosis. Total urinary output was collected, preserved with toluene, and daily determinations of total urinary nitrogen<sup>13, 14</sup> checked by macro- and micro-Kjeldahl methods, nonprotein nitrogen and urea nitrogen<sup>15</sup> were made. At intervals of every two days, blood plasma protein,<sup>13</sup> urea nitrogen,<sup>16</sup> and nonprotein nitrogen<sup>13</sup> levels were determined. The usual procedure was to keep the patient on a preliminary protein starvation regime for four or five days to allow urinary nitrogen to reach a basal level, then to give whole human or bovine plasma intravenously for a five-day period followed by another period of protein starvation.

Table XII illustrates the effect of intravenous administration of bovine serum on nitrogen metabolism. In the basal period, Jan. 3, 1941, through Jan. 8, 1941, this patient did not reach as low a urinary nitrogen excretion as most of our studies have shown. Usually after ade-

TABLE XIII  
NITROGEN BALANCE ATTENDING INTRAVENOUS ADMINISTRATION OF HUMAN PLASMA\*

PERIOD	URINE			BLOOD			AVERAGE DAILY CALORIC INTAKE	NITROGEN INTAKE AS HUMAN PLASMA INTRAVENOUSLY (G.)	WEIGHT (KG.)
	TOTAL N <sub>2</sub> (GM.)	N.P.N. (GM.)	UREA N <sub>2</sub> (GM.)	TOTAL PROTEIN (GM.)	N.P.N. (MG. %)	B.U.N. (MG. %)			
9/9/40	25.01	21.96	17.17	6.03	28.2	11.7	600	0	45.0
9/12/40									
Average daily	6.26	6.21	1.29	6.09	26.0	11.7	600	Total N <sub>2</sub> 2,500 Average daily 5.6	41.2
9/13/40-9/17/40	21.88	22.00	13.80						
Average daily	1.37	1.1	2.76	6.38	30.3	11.2	1,000	0	41.3
9/18/40-9/22/40	16.95	16.97	9.53						
Average daily	3.39	3.39	1.90						

\*Mr. J. O. (U. H. 695429), aged 51 years, carcinoma of colon.

TABLE XII  
NITROGEN BALANCE STUDIES ATTENDING INTRAVENOUS ADMINISTRATION OF BOVINE SERUM\*

PERIOD	URINE			BLOOD			DAILY CALORIC INTAKE	NITROGEN INTAKE AS BOVINE SERUM INTRAVENOUSLY (G.C.)	WEIGHT (KG.)
	TOTAL N <sub>2</sub> (GM.)	N.P.N. (GM.)	UREA N <sub>2</sub> (GM.)	TOTAL PROTEIN (GM.)	N.P.N. (MG. %)	B.U.N. (MG. %)			
1/3/41- 1/8/41	47.32	47.22	28.54	5.62	23.0	10.5	1,500	0	51.8
Average daily 1/9/41- 1/13/41	7.88 31.53	7.86 34.51	4.91 17.28	6.19	23.3	15.0	1,500	Total N 2,500 Average daily 30.75 Gm. 6.15 Gm.	51.8
Average daily 1/14/41- 1/17/41	6.91 25.80	6.90 25.37	3.46 13.73	5.95	32.0		1,500	0	51.3
Average daily	6.15	6.34	3.43						

\*Mr. O. W. (U.H. 702623), aged 48 years, carcinoma of colon.

\*Mr. O. W. (U.H. 702623), aged 18 years, carcinoma of colon.

†Patient developed general urticaria and edema lasting 2 days, from 1/15/41 to 1/17/41.

tion of epinephrine in amounts of 0.5 to 1 c.c. The other reactions of less severe magnitude occurred with larger doses and appeared at variable times after the start of the injection or even several hours after the completion of the injection. If a patient tolerates the small initial doses, there is probably no great natural sensitivity, and the reactions to a larger dose are not of such severe nature. Although the incidence of reactions was reduced from 66.6 per cent with whole serum to 24.5 per cent by adsorption with human red blood cells, their incidence and magnitude were still sufficient to contraindicate any clinical use of whole bovine serum or plasma at the present time. Also, this modification does not insure against the anaphylactic type of reaction for one of the three cases was in the adsorbed group.

The reaction that occurs with adsorption by human red blood cells apparently is not specific to the various groups of red blood cells or to the blood group of the recipient, but the adsorption may remove a species specific substance in the bovine serum capable of producing untoward symptoms in a foreign host. It is not likely that removal of hemolysins, as such, is an important factor in reactions, as they are not present in sufficiently high concentrations to be active, when diluted in the blood stream of the recipient, and reactions, when they did occur, were not attended by jaundice or hemoglobinuria. A more likely possibility, therefore, would be that adsorption removes some reaction-producing substance in addition to, or as a corollary of, removing hemolysins and hemagglutinins. This explanation may account satisfactorily for the observation that kaolin, although its use reduced the incidence of reactions somewhat, was not as effective an adsorbing agent as red blood cells.

One might surmise that with the added experience and improvement in technique of preparation of plasma and serum gained over a period of eighteen months, the latter products would reflect a lower incidence of reactions. Hence the results with adsorbed serum might be interpreted as more apparent than real. However, this was not the case, for the results with the use of whole bovine serum, also prepared in the latter months of this study after the technique of preparation was well standardized, do not show a similar improvement over our earlier experiences when plasma was used.

Delayed reactions of the serum sickness type were a frequent occurrence in our series, occurring in 43 of 81 patients followed. There did not appear to be any very significant difference in its incidence in any of the groups studied. Very few joint manifestations were noted, the principal complaints being urticaria with occasional gastrointestinal upsets and low-grade fever. The onset varied from two to ten days after the final injection, and symptoms subsided usually after forty-eight to seventy-two hours. It is of interest that no instance of serum sickness occurred until serum or plasma injections were discontinued.

quate starvation, the urinary nitrogen reaches levels of 3 to 4 Gm. daily. Following this initial starvation period, 500 c.e. of adsorbed bovine serum was given intravenously daily. Total nitrogen analysis of this serum showed 1.23 Gm. per 100 c.e. (7.68 Gm. protein per 100 c.e.). Although positive nitrogen balance is not attained, it is noted that the average daily urinary nitrogen excretion decreased during this period over the basal period (6.91 Gm. nitrogen to 7.88 Gm. nitrogen) while 30.75 Gm. of nitrogen in the form of plasma protein was given intravenously. No protein appeared in the urine. In the subsequent period of nonprotein intake, there was no delayed spillage of nitrogen as indicated by an average daily excretion of 6.45 Gm. nitrogen. There was a slight increase of the plasma protein level from 5.62 at the end of the initial starvation period to 6.19 Gm. per 100 c.e. at the end of the injection period. Also, there did not appear to be any shift of the urea nitrogen-nonprotein nitrogen ratio which might indicate an abnormal catabolism of protein. It would appear, therefore, that this protein, given intravenously to man, is certainly retained by the body for nitrogen metabolism or for replenishment of protein stores.

In a similar study using whole human plasma (Table XIII), positive nitrogen balance was obtained in three consecutive cases. During the starvation period, Sept. 9, 1940, through Sept. 12, 1940, there was an average daily urinary nitrogen excretion of 6.26 Gm. In the five-day period, Sept. 13, 1940, through Sept. 19, 1940, when 2,500 c.e. of whole human plasma containing 28 Gm. nitrogen was given intravenously, only 21.88 Gm. of nitrogen appeared in the urine, or an average daily urinary nitrogen excretion of 4.37 Gm. In the subsequent starvation period, the average daily nitrogen excretion was 3.39 Gm. nitrogen, indicating that the plasma protein injected intravenously is retained by the body. Since there was no significant rise in the plasma protein level of the patient, while an amount of plasma protein about equal to his total circulating plasma protein was given, this must have been taken out of the circulation and used for nitrogen metabolism or for replenishing the protein stores. Pommerenke and co-workers<sup>17</sup> have reported maintenance of dogs in positive nitrogen balance by intravenous administration of dog plasma but failed to note utilization of a heterologous protein (horse serum) in dogs.

#### DISCUSSION

Bovine plasma and serum can be given to man and even though its use has been attended with a high incidence of reactions, in only 3 out of 120 patients were the reactions of such magnitude as to jeopardize the life of the recipient. In our hands there have been no fatalities. These three severe anaphylactic reactions occurred with small doses, 0.1 c.e., 0.1 c.e., and 2 c.e. of bovine serum or plasma and appeared almost immediately. All responded to prompt intravenous administra-

9. Cohn, E. J.: Properties and Functions of Plasma Proteins With Consideration of Methods for Their Separation and Purification, *Chem. Rev.* 28: 395-417, 1941.
10. Janeway, C. A., and Beeson, P. B.: Use of Purified Bovine Albumin Solution as Plasma Substitute, *J. Clin. Investigation* 20: 435, 1941.
11. Keys, A., Taylor, H. L., and Savage, G. M.: Letter to J. A. M. A., *J. A. M. A.* 117: 62, 1941.
12. Strumia, M. M., and McGraw, J. J.: Frozen and Dried Plasma for Civil and Military Use, *J. A. M. A.* 116: 2378-2382, 1941.
13. Hawk, P. B., and Bergeim, O.: *Practical Physiological Chemistry*. Philadelphia, 1931, P. Blakiston's Son & Co., p. 814.
14. Koch, F. C., and McMeekin, T. L.: New Direct Nesslerization Micro Kjeldahl Method and a Modification of the Nessler-Folin Reagent for Ammonia, *J. Am. Chem. Soc.* 46: 2066-2069, 1924.
15. Folin, O., and Youngberg, G. E.: Note on Determination of Urea in Urine by Direct Nesslerization, *J. Biol. Chem.* 38: 111-112, 1918.
16. Karr, W. G.: A Method for the Determination of Blood Urea Nitrogen, *J. Lab. & Clin. Med.* 9: 329-333, 1924.
17. Pommerenke, W. T., Slavin, H. B., Kariher, D. H., and Whipple, G. H.: Dog Plasma Protein Given by Vein Utilized in Body Metabolism of Dog: Horse Plasma and Dog Hemoglobin Not Similarly Utilized, *J. Exper. Med.* 61: 283-297, 1935.



Apparently repeated daily injections of bovine serum for six or seven days prevented the onset of serum sickness until cessation of injections after which it appeared in several days.

It would appear that the use of bovine plasma proteins in clinical states of shock or depleted protein stores may have real value, in those patients who can tolerate it, to provide a source of parenteral nitrogenous alimentation as well as to combat the contracted blood volume of shock. Further trial with preparations of bovine albumin may eliminate reactions sufficiently to establish the albumin fraction of bovine plasma as a safe and practical blood substitute for the treatment of contracted blood volume and protein states in man. As yet, however, the injection of bovine plasma or one of its fractions must be looked upon as an experimental project.

#### SUMMARY

1. Our experiences with the use of whole bovine serum and plasma in 120 patients are reported. The incidence of reactions was sufficient to contraindicate any clinical use of whole bovine serum or plasma at the present time.

2. Bovine plasma and serum are shown to contain hemolysins and hemagglutinins to human red blood cells. Most of the hemolysins and about 50 per cent of the hemagglutinins can be removed by adsorption on human red blood cells. By so doing, the incidence of reactions was reduced from 66.6 to 24.5 per cent.

3. Positive nitrogen balance can be attained by intravenous administration of human plasma and can be approached closely with intravenous administration of whole bovine plasma. Both are apparently retained and utilized by the body.

4. The preparation of a satisfactory product of bovine albumin, from which the globulin fraction has been eliminated completely, may prove a safe and practical blood substitute.

#### REFERENCES

1. Blalock, A., and Mason, M. F.: *Blood and Blood Substitutes in Treatment and Prevention of Shock: With Particular Reference to Their Use in Warfare*, Ann. Surg. 113: 657-677, 1941.
2. Hartman, F. W., Schilling, V., Harkins, H. N., and Brush, B.: *Pectin as a Blood Substitute*, Ann. Surg. 114: 212-226, 1941.
3. Davis, H. A., and Blalock, Jr., J. F.: *Autologous and Homologous Transfusion of Human Ascitic Fluid*, J. Clin. Investigation 18: 219-225, 1939.
4. Amberson, W. R.: *Blood Substitutes*, Biol. Rev. 12: 48, 1937.
5. Shortell, J. H., Cotting, W. F., and Leary, T.: *The Treatment of Wounds With Normal Beef Serum*, Boston M. & S. J. 177: 622-627, 1917.
6. Penna, J., Cuena, J. B., and Kraus, R.: *Treatment of Anthrax in Man With Normal Serum*, Prensa méd. Argent. 28: 297-299, 1917.
7. Wangensteen, O. H., Hall, H., Kremen, A. J., and Stevens, B.: *Intravenous Administration of Bovine and Human Plasma: Proof of Utilization*, Proc. Soc. Exper. Biol. & Med. 43: 616-621, 1940.
8. Kremen, A. J., Taylor, H. L., and Hall, H.: *Skin Sensitivity of Man to Bovine Plasma and Its Albumin and Globulin Fractions*, Proc. Soc. Exper. Biol. & Med. 43: 532-533, 1940.

consisted in striking one of the posterior extremities a number of blows with a blunt instrument. After the trauma had been produced the injured extremity was surrounded by ice packs in approximately one-half of the experiments and by bags containing hot water in the others. The blood pressure was determined by arterial cannulation and the use of a mercury manometer. The hematocrit determinations were made by the use of Van Allen tubes. The locations in which temperature readings were made in most of the experiments included the rectum, the peritoneal cavity (through a small stab incision), and the subcutaneous tissues of the axilla and of the injured extremity. In most instances the animals were observed until death occurred, and the loss of blood and fluid into the injured part and the adjacent tissues was determined by the bisection method which has been described previously.<sup>3</sup> The experiments are divided into groups according to the anesthetic agent that was used.

#### *Nembutal Anesthesia.*—

1. Application of Heat: Fourteen experiments of this type were performed. The average duration of life was five hours and fifty-two minutes, and the average difference in the weights of the traumatized and nontraumatized parts was 3.80 per cent of the body weight. The average elevations of temperature were as follows: rectal, +5.7° F.; peritoneal cavity, +6.7° F.; axillary, +4.8° F.; and injured leg, +7.6° F.

2. Application of Cold: There were seventeen such experiments. One of the animals did not develop shock and was killed after twenty-two hours, the difference in the weights of the two posterior parts being 2.83 per cent of the body weight. In the remaining sixteen experiments the average duration of life was thirteen hours and thirty-two minutes, and the average difference in the weights of the traumatized and nontraumatized parts was 3.98 per cent of the body weight. The average depressions of the temperature were as follows: rectal, -15.8° F.; peritoneal cavity, -5.9° F.; axillary, -7.0° F.; and injured leg, -48.0° F.

#### *Barbital Anesthesia.*—

1. Application of Heat: Six experiments of this type were performed. The average duration of life was five hours and forty-four minutes, and the average difference in the weights of the injured and uninjured parts was 4.05 per cent of the body weight. The average elevations of temperature were as follows: rectal, +4.9° F.; peritoneal cavity, +6.6° F.; axillary, +4.7° F.; and injured leg, +8.0° F.

2. Application of Cold: There were six experiments of this type. The average survival period was eight hours and fifty-four minutes, and the average difference in the weights of the injured and uninjured parts was 3.58 per cent of the body weight. The average depressions of temperature were as follows: rectal, -12.2° F.; peritoneal cavity, -10° F.; axillary, 10.0° F., and leg, -45.8° F.

# A COMPARISON OF THE EFFECTS OF THE LOCAL APPLICATION OF HEAT AND OF COLD IN THE PREVENTION AND TREATMENT OF EXPERIMENTAL TRAUMATIC SHOCK

ALFRED BLALOCK, M.D., BALTIMORE, MD.

(From the Departments of Surgery of Johns Hopkins University, Baltimore, Md., and of Vanderbilt University, Nashville, Tenn.)

IN A PREVIOUS paper<sup>1</sup> the effects on animals in shock of causing rather pronounced elevations or depressions of the body temperature by the general application of heat or cold were reported. It was noted that significant elevations of temperature decrease the chance of life and shorten the period of survival. The application of cold does not increase the chance of survival but is accompanied with a lengthening of the survival of an animal with a low blood pressure. The studies showed that significant elevations above normal of the temperature of animals in shock cause more disastrous effects than do depressions of similar degree. It was pointed out that in shock there is not an identical reduction in the flow of blood to all tissues, that the flow to the extremities is more reduced than that to the more vital structures, and that the causation of general peripheral vasodilatation by the application of heat may result in harmful effects. It was concluded that vigorous efforts to elevate the body temperature should not be undertaken in secondary shock unless at the same time one causes an increase in the blood volume by the introduction of whole blood or a suitable substitute for it.

In the previous experiments<sup>1</sup> the application of heat or cold was general. In the present studies, in which shock was produced by gross trauma to an extremity, the application of heat or cold was limited to the injured part and an effort was made to compare the effects of the two agents. In this connection it is to be noted that Allen<sup>2</sup> found that constriction of the circulation of the thigh is more likely to be followed by the development of shock if the temperature is high than if it is low.

## METHODS AND RESULTS

Large animals were used in all experiments. Pain was prevented by the use of suitable anesthetic agents: nembutal 25 to 30 mg. per kilogram of body weight in some experiments, barbital 0.3 Gm. per kilogram of body weight in some, and morphine supplemented by the inhalation of ether during the period of traumatization in others. An additional dose of the anesthetic agent was administered if the degree of the anesthesia became light. The method which was used for producing shock

consisted in striking one of the posterior extremities a number of blows with a blunt instrument. After the trauma had been produced the injured extremity was surrounded by ice packs in approximately one-half of the experiments and by bags containing hot water in the others. The blood pressure was determined by arterial cannulation and the use of a mercury manometer. The hematocrit determinations were made by the use of Van Allen tubes. The locations in which temperature readings were made in most of the experiments included the rectum, the peritoneal cavity (through a small stab incision), and the subcutaneous tissues of the axilla and of the injured extremity. In most instances the animals were observed until death occurred, and the loss of blood and fluid into the injured part and the adjacent tissues was determined by the bisection method which has been described previously.<sup>3</sup> The experiments are divided into groups according to the anesthetic agent that was used.

#### *Nembutal Anesthesia.*—

1. Application of Heat: Fourteen experiments of this type were performed. The average duration of life was five hours and fifty-two minutes, and the average difference in the weights of the traumatized and nontraumatized parts was 3.80 per cent of the body weight. The average elevations of temperature were as follows: rectal,  $+5.7^{\circ}$  F.; peritoneal cavity,  $+6.7^{\circ}$  F.; axillary,  $+4.8^{\circ}$  F.; and injured leg,  $+7.6^{\circ}$  F.

2. Application of Cold: There were seventeen such experiments. One of the animals did not develop shock and was killed after twenty-two hours, the difference in the weights of the two posterior parts being 2.83 per cent of the body weight. In the remaining sixteen experiments the average duration of life was thirteen hours and thirty-two minutes, and the average difference in the weights of the traumatized and nontraumatized parts was 3.98 per cent of the body weight. The average depressions of the temperature were as follows: rectal,  $-15.8^{\circ}$  F.; peritoneal cavity,  $-5.9^{\circ}$  F.; axillary,  $-7.0^{\circ}$  F.; and injured leg,  $-48.0^{\circ}$  F.

#### *Barbital Anesthesia.*—

1. Application of Heat: Six experiments of this type were performed. The average duration of life was five hours and forty-four minutes, and the average difference in the weights of the injured and noninjured parts was 4.05 per cent of the body weight. The average elevations of temperature were as follows: rectal,  $+4.9^{\circ}$  F.; peritoneal cavity,  $+6.6^{\circ}$  F.; axillary,  $+4.7^{\circ}$  F.; and injured leg,  $-8.0^{\circ}$  F.

2. Application of Cold: There were six experiments of this type. The average survival period was eight hours and fifty-four minutes, and the average difference in the weights of the injured and noninjured parts was 3.58 per cent of the body weight. The average depressions of temperature were as follows: rectal,  $-12.2^{\circ}$  F.; peritoneal cavity,  $-10^{\circ}$  F.; axillary,  $-10.0^{\circ}$  F., and leg,  $-45.8^{\circ}$  F.

*Morphine-Ether Anesthesia.*—

1. Application of Heat: There were five experiments of this type. The average survival period was five hours and fifty minutes, and the average difference in the weights of the two parts was 3.40 per cent of the body weight. The average elevations of temperature were as follows: rectal,  $+5.3^{\circ}$  F.; and peritoneal cavity,  $+6.5^{\circ}$  F.

2. Application of Cold: There were seven of these experiments. The average survival period was eight hours and thirty-nine minutes, and the average difference in the weights of the injured and noninjured parts was 3.73 per cent of the body weight. The average decline of the rectal temperature was  $-8.8^{\circ}$  F., and that of the temperature of the peritoneal cavity was  $-3.1^{\circ}$  F.

If the groups are combined, the differences in anesthetic agents being ignored, there were twenty-five experiments in which heat was applied locally following trauma to an extremity and twenty-nine experiments in which cold was applied. The following results were obtained: Average survival periods: (1) heat, 5 hours and 49 minutes; and (2) cold, 11 hours and 24 minutes. Average differences in weights of traumatized and nontraumatized parts in percentages of body weight: (1) heat, 3.78; and (2) cold, 3.84. Average alteration in temperature in degrees Fahrenheit: rectal, (1) heat,  $+5.4$ , and (2) cold,  $-12.7$ ; peritoneal cavity, (1) heat,  $+6.6$ , and (2) cold,  $-6.1$ ; axilla, (1) heat,  $+4.8$ , and (2) cold,  $-7.8$ ; injured leg, (1) heat,  $+7.7$ , and (2) cold,  $-47.4$ .

It should be noted that the local applications of heat and of cold were made to the injured extremity and thus the temperature of the part would be expected to be altered greatly, as was the case. Furthermore, the containers which held the hot water or the ice were in fairly close proximity to the rectal region and undoubtedly there was some direct effect on the rectal temperature. The most significant readings are probably those which were recorded in the peritoneal cavity. It is of interest that the temperature of the abdominal cavity increased slightly in several of the experiments in which ice was applied to an extremity.

Alterations in the hematocrit readings were not great in any of the experiments. There was usually a slight increase in the concentration of the red blood corpuscles in the studies in which heat was applied and a slight dilution in the experiments in which cold was applied. These results suggest that the heat caused an increase in capillary permeability.

## COMMENT

Before these experiments were undertaken it was hoped that the local cooling of the injured part would lessen the escape of blood and fluid into the traumatized area and the adjacent tissues. The results do not indicate that such is the case since the loss in these studies was almost identical with that noted in the experiments in which heat was applied. It is possible that the escape of fluid into the injured tissues would have been lessened had the part been cooled more rapidly.

It is of interest that the average survival period of the animals in the group in which cold was applied was twice that of the group in which an elevation of body temperature was caused by the local application of heat. The results are similar to those reported previously by Mason and myself<sup>1</sup> on the effects of the general application of heat and cold.

Emphasis is to be placed on the fact that these experiments offer no evidence whatever that shock should be treated by causing a depression of the body temperature. The experiments do show very clearly that the survival time is shortened by the local application of heat which is of sufficient degree to cause a marked general elevation of the body temperature. It is likely that a marked rise in the temperature of the tissues is accompanied by vasodilatation and an increase in capillary permeability. It would appear that one is warranted in concluding that extreme degrees of heat should not be used even locally in the treatment of shock, particularly if means are not immediately available for increasing the blood volume by the introduction of blood or a suitable substitute.

It is probably unnecessary to mention the fact that the experimental conditions reported here may be somewhat different from the conditions that are present in shock in man. The response to alterations in temperature may be somewhat different in animals and in man. Dogs dissipate heat, in the main, by panting. In these studies anesthesia was necessary, whereas this complicating factor may not be a part of the picture in traumatic shock in patients. Furthermore, the temperature of the animals was normal at the beginning of the experiments, whereas exposure to inclement weather may have lowered the temperature of the patient. It is agreed that the patient who has been exposed to cold and moisture should be placed in a warm bed and should be covered with blankets. On the other hand, the indiscriminate use of large numbers of hot-water bottles and other heating devices may result in harm rather than in improvement in the general condition of the patient.

It is a pleasure to express my thanks to Dr. Barney Brooks for his helpful advice.

#### REFERENCES

1. Blalock, Alfred, and Mason, M. F.: A Comparison of the Effects of Heat and Those of Cold in the Prevention and Treatment of Shock, *Arch. Surg.* 42: 1054, 1941.
2. Allen, F. M.: Surgical Considerations of Temperature in Ligated Limbs, *Am. J. Surg.* 45: 459, 1939.
3. Blalock, Alfred: Experimental Shock. The Cause of the Low Blood Pressure Produced by Muscle Injury, *Arch. Surg.* 20: 959, 1930.

# A STUDY OF GASTROINTESTINAL MOTILITY IN THE DOG FOLLOWING ILEOCOLOSTOMY AND PARTIAL COLONIC RESECTION

DONALD D. KOZOLL,\* M.D., AND H. NECHIELES, M.D., PH.D.,  
CHICAGO, ILL.

*(From the Department of Gastro-Intestinal Research, Michael Reese Hospital)*

THE rationale upon which the anastomotic procedures of the ileum and colon are based is that by diversion of the fecal stream past the site of pathology, physiologic rest will be attained. The benefits to be accrued from this include subsidence of inflammatory reactions localization of infectious processes, decreased absorption of toxic products from the involved segment, relief from obstruction, decompression, and general rehabilitation in preparation for further surgery.

The procedure of ileocolostomy has been recommended for a multitude of pathologic processes involving the right half of the colon and the terminal segment of the ileum. The anastomosis alone has been advocated as a curative procedure in some instances; in others, it is recommended as the first stage in preparation for resection of the right half of the colon. Lewison,<sup>1</sup> Colp,<sup>2</sup> Berg,<sup>3</sup> Crohn,<sup>4</sup> and others have been advocates of ileocolostomy as the surgical procedure of choice in the treatment of regional (segmental, terminal) ileitis. Colp has utilized it for treatment of regional colitis, and many others have long used it for tuberculosis of the ileocecal region and for obstructive lesions of the terminal ileum. Rankin and Graham<sup>5</sup> and Lahey<sup>6</sup> favor completion of an ileocolostomy in preparation for resections of the right half of the colon, and the former have described an aseptic technique for its completion.<sup>7</sup>

A fair amount of clinical evidence exists to indicate that short-circuiting operations upon the ileum and colon do not actually lead to physiologic rest of the proximal colon left behind. Case<sup>8</sup> in 1915 reviewed approximately forty cases of ileocolostomy performed by different surgeons and observed retrograde passage of a barium meal into the blind loop of the colon to be the rule. He frequently noted that the barium content in that area frequently became impacted and that occasionally dilatation of the terminal resected ileum progressed to a point where it assumed the size of the colon. Furthermore, because of the case with which barium enemas regurgitated into the ileum following the anastomosis, he urged the necessity for the reconstruction of a sphincteric mechanism at the site of the new anastomosis. Ginzburg, Colp, and

\*Bernard Portis Research Fellow in Surgery.  
Received for publication, July 5, 1941.

Sussman<sup>2</sup> reviewed the roentgenograms of thirty-two cases of ileocolostomy and although they found regurgitation of ileal contents into the excluded segment of colon, this did not lead to abnormal distention, dilatation, or ulceration. Berg<sup>3</sup> recognized that an ileosigmoidostomy did not divert the fecal stream because of continued retrograde peristalsis and accordingly recommended division of the sigmoid at a point proximal to the anastomosis, followed by a resection of the entire excluded colon at a subsequent date.

However, there is little or no experimental work to clarify the question of whether short-circuiting procedures of the colon produce physiologic rest. In addition to that question, there is much more to be learned concerning the fate of the blind loop of colon and the stump of ileum, the effect of pouring liquid feces into the distal portions of the colon, the effects of such procedures on colonic filling and emptying, the compensatory function of the distal colon following resection of one-half or more of the colon, and finally, the influence of these procedures upon the general body economy of the animal.

#### METHOD

A colony of eleven large, carefully selected, healthy normal dogs were selected and prepared for chronic experimentation. Each animal had an individual kennel, was fed individually, and was given antihelminth medication upon arrival (tetrachlorethylene-magnesium sulfate). Feedings of a standard quantity and quality diet<sup>\*</sup> were given at 9:00 A.M. daily and the animals permitted in outdoor kennels after eating for exercise and defecation. The beneficial effects of this type of care on the general condition of the animal and on the surgical risks were obvious. The animals were trained to lie quietly on a fluoroscopy table.

At weekly intervals, the dogs were fed a barium meal at the time of the usual meal, and the animals fluoroscoped at hourly intervals thereafter for the remainder of that day (eight to nine hours). Records of the passage of the barium meal were kept on specially prepared mimeographed sheets (Fig. 3) and the amounts of barium present in the stomach, small intestines, and colon at each observation were recorded in percentage of the total. The barium meal consisted of 70 Gm. of barium sulfate, mixed well with 150 c.c. of water and one 16 ounce can of dog food.<sup>†</sup> On the second day the dogs were fed their usual meal at the customary hour, allowed to defecate, and then fluoroscoped at intervals until all barium was evacuated. Usually, eating of the second meal served as the stimulus for complete evacuation of all barium accumulated in the colon overnight.

<sup>\*</sup>A standard meal included the following: One 16 ounce can of commercial dog food, one 12 ounce glass of milk, five slices wheat bread, one tablespoon cod-liver oil, one-half tablespoon powdered brewer's yeast, one teaspoon bone meal.

<sup>†</sup>The meal was eaten by the animals avidly. This is important, because results are irregular when a barium meal is given by stomach tube.<sup>2</sup>



## RESULTS

*Normal Controls.*—Fifty-two motor meal studies were made at weekly intervals on eleven normal dogs. Fig. 3 is a presentation of the average rate of progress of the barium meals in all dogs. Variations between different animals proved no greater than variations in the same animals, which were slight, so that the values given in Fig. 3 represent results seen in the great majority of instances.

Gastric emptying usually commenced from within one-half to one hour after giving the meal, and emptying was complete between six and eight hours. The small intestines never contained more than 40 per cent of the barium at any time and the barium usually traversed it from seven to nine hours after the eating of the meal. The normal colon began to fill with barium between the fourth and sixth hour and was completely filled at the eighth or ninth hour. Depending upon the habits of the individual animal, some were inclined to defecate barium as soon as the colon began to fill, whereas the majority retained the barium in the colon until permitted outdoors to defecate. Upon defecation, the distal colon emptied itself first, followed by an immediate passage downward of the contents of the proximal colon into the distal portions. Evacuation was usually complete in twenty-four to thirty hours, especially following the eating of a second meal. These studies served as the preoperative controls.

The progress of barium through the gastrointestinal tract of the dog compares very favorably with figures given for the human being by Brown and Sampson.<sup>10</sup>

Barium enemas were given to the same animals to determine the degree of colonic filling and the competency of the ileocecal sphincter. These studies were intended to serve as controls for the barium enemas to be given following ileocolostomy. The enemas were administered under measured pressure from a bottle, attached to which was a pressure bulb and a tyco's manometer for measuring the pressures attained.

In only three of the eleven dogs were the ileocecal sphincters consistently competent against regurgitation of the enema under slight pressure. The colon would frequently hold between 600 and 900 c.c. of solution, depending upon the size of the animal. Intracolonic pressures attained for a period of several minutes varied between 30 and 50 mm. In over 70 per cent of the animals the sphincter "gave" at this pressure. The pressure within the colon usually fell when regurgitation into the ileum occurred. It must be appreciated that such pressures are not normally developed, except perhaps under conditions of mechanical obstruction. Evacuation of the barium enema from the colon was usually complete; regurgitated material left the ileum in about the same length of time as in the case of a meal.

*Observations Following Ileocolostomy.*—End-to-side ileocolostomies were performed under aseptic operative conditions on all eleven dogs under intravenous nembutal (pentobarbital) anesthesia, with two deaths (18 per cent mortality). Figs. 1 and 2 illustrate the procedure employed. We have combined the end-to-side ileocolostomy as described by Rankin and Graham<sup>5,7</sup> with the aseptic technique of gastrointestinal anastomoses as described by Wangensteen.<sup>11</sup> Division of the ileum was made at a point 5 to 8 cm. distant from the ileocecal junction, for at this level of the ileum there is frequently a branch of the cecal artery and vein which courses along the antimesenteric border of the ileum of the dog; it was utilized to increase the collateral blood supply of the anastomosis.

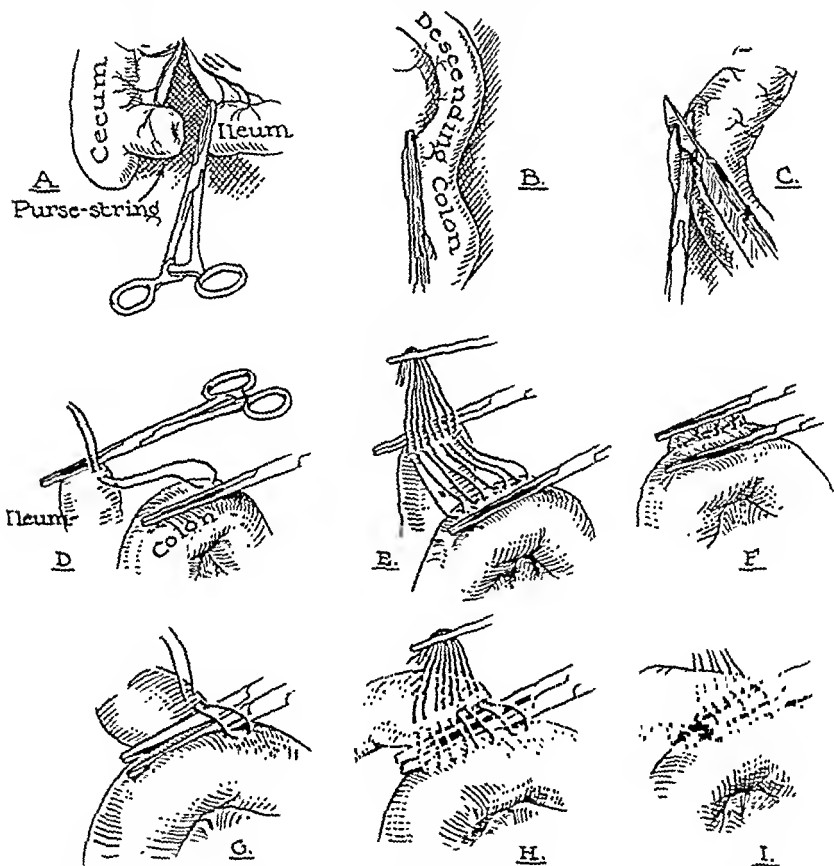


Fig. 1.—Author's modification of end-to-side ileocolostomy. A, Ileum severed 5 to 8 cm. distal to ileocecal junction to take advantage of branch of ileocecal artery usually seen on antimesenteric surface of ileum at this level (not shown in this drawing). B, Stoma on colonic side of anastomosis created by clamping small nipple on antimesenteric border. C, Nipple removed with scalpel, cauterization with phenol and cut on posterior surface. D, First interrupted Halsted mattress suture with No. 00.00 intestinal catgut on posterior surface. Sutures placed in longitudinal axis of intestine and stitch of ileum and colon. Four such sutures are adequate (E). F, Posterior row of interrupted sutures. G and H, Four similar sutures constitute anterior row. I, Inversion to free that amount of ileum and colon at a time by gradually withdrawing clamps anastomosis is assured.

Inversion of the distal ileal stump was accomplished by a purse-string suture of No. 0000 intestinal catgut followed by three or four interrupted Halsted mattress sutures of silk which inverted the first row of sutures. The last silk suture was taken through the undersurface of the cecum to bring it down as a hood over the inverted ileum. The anastomosis of the end of the ileum to the site of the colon was accomplished with two straight-bladed intestinal clamps of small enough caliber to minimize

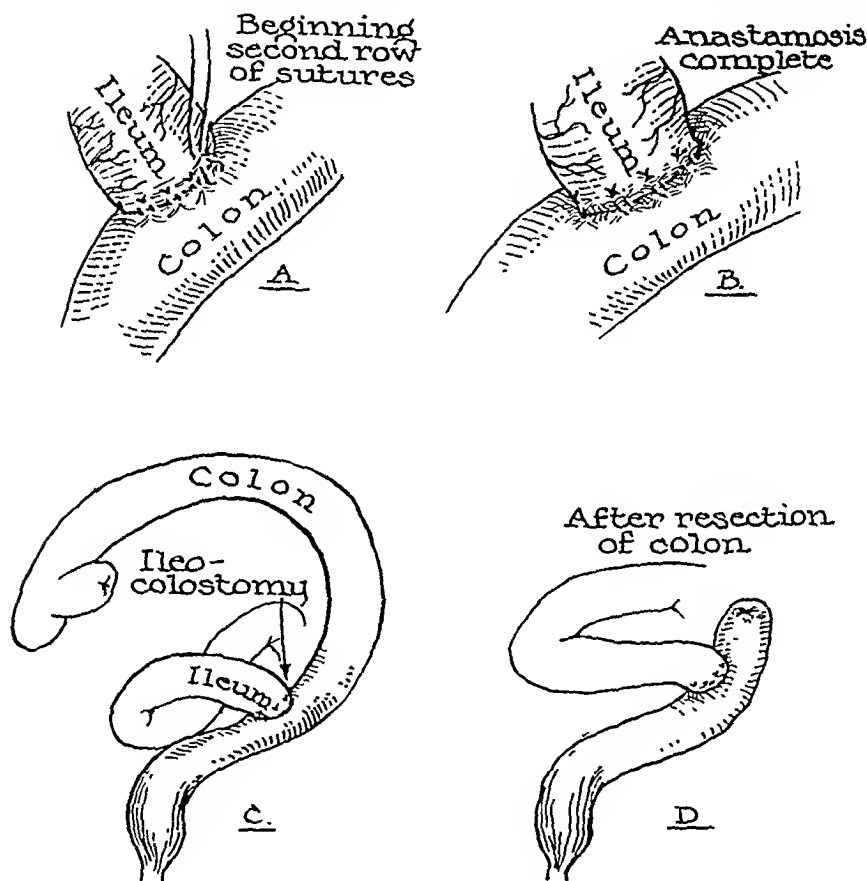


Fig 2—A. Second row of interrupted Halsted mattress sutures of silk are placed around the circumference of the anastomosis, inverting the previous row of catgut sutures. B. The completed anastomosis. C. The postoperative appearance of the ileum and colon. The anastomosis is usually wrapped in omentum. D. The appearance of the proximal excluded colon. Inversion of the same method used for the anastomosis.

the amount of intestine crushed. The first posterior rows of sutures usually consisted of four interrupted Halsted mattress sutures of No. 0000 intestinal catgut on a small curved atraumatic needle. (Fig. 1) The sutures were taken along the long axis of both structures, that on the colonic side incorporating about twice as much tissue to overcome the disproportion in the size of the two structures. Similar sutures were

then placed on the anterior surfaces and tied as the two intestinal clamps were gradually withdrawn. A second and final row of similarly interrupted sutures of fine silk were then taken around the circumference of the entire anastomosis. (Fig. 2.) The advantages of the interrupted sutures in this procedure over the continuous sutures as originally described by Rankin<sup>7</sup> lies in the ability to withdraw the intestinal clamps gradually instead of risking spillage of intestinal content as we have frequently otherwise noted. It further decreases the amount of enoerachment upon the caliber of the anastomosis, and provides the greater safety inherent in the use of interrupted sutures. Approximately 2 Gm. of

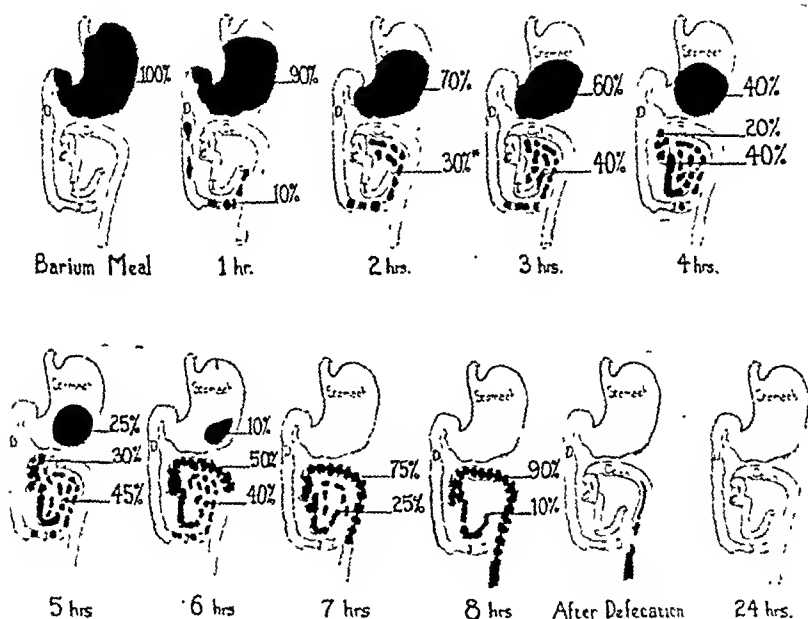


Fig. 2.—Record of average progress of motor meal in normal control dogs as drawn from fluoroscopy. Note that normal colon begins to fill between the fourth and sixth hours and is almost completely filled by the eighth hour. Colon is usually emptied after twenty-four hours if defecation is encouraged by eating. Asterisk denotes percentage of barium in small intestines.

sulfanilamide powder was applied to the serosal surface of the anastomosis, the anastomosis wrapped in omentum and returned to the peritoneum, and closure effected in layers. All animals were given intravenous fluids postoperatively as needed, usually until the third day. Sulfanilamide solution (0.8 per cent in saline solution) was administered subcutaneously for the same period of time. Fluids by mouth were usually begun on the second postoperative day. By the end of the week the animals were returned to their usual diet which they consumed with great appetite. No immediate postoperative complications were

countered. After the first week, all stools were formed and were normal in color and character. An interval of at least two weeks elapsed between operation and the first barium meal.

A total of fifty-four barium meal studies were carried out at weekly intervals on the nine dogs which survived the operation. Fig. 4 is a composite representation of the average progress of all barium meals in all dogs following ileocolostomy. The most striking observation was the effect of ileocolostomy upon the time of filling of the colon; whereas in the normal controls this occurred between the fourth and sixth hours,

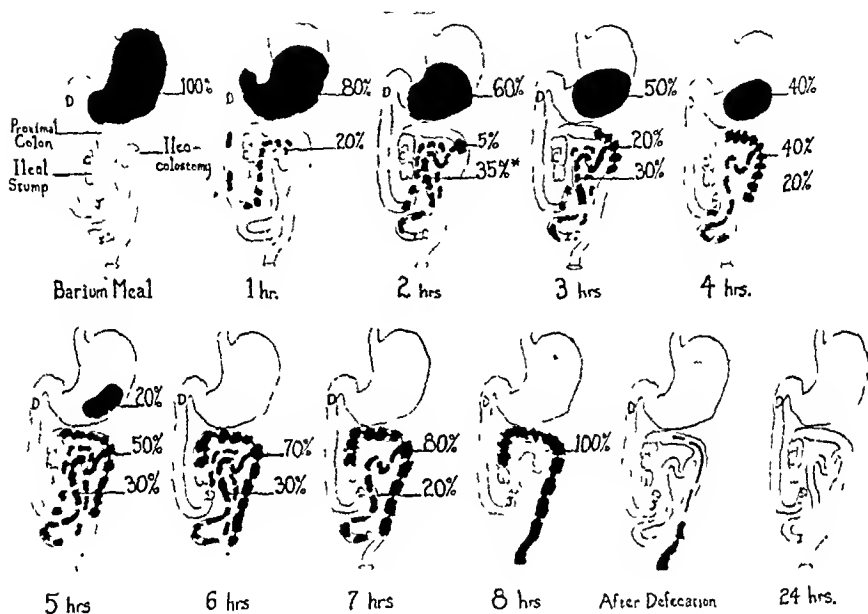


Fig. 4.—Recovery of motor meal in same series of dogs as represented in Fig. 2 as drawn from fluoroscopy. Note that gastric emptying time is 10 minutes. Note that colonic filling commenced two hours earlier than in the normal control and was completed by the sixth hour. Note especially that retrograde passage of barium into proximal excluded colon occurred at same rate as filling of the distal colon. Emptying time of the colon was the same as prior to surgery. Asterisk denotes percentage of barium in small intestines

after ileocolostomy filling was found to commence between the second and fourth hours. This two-hour difference was seen in the majority of instances, the exception being a difference of less than two hours. In no case was the time of colonic filling the same as preoperatively or prolonged. The interval of time between operation and motility tests appeared to make no difference, the longest interval being four months. Ginzburg, Colp, and Sussman<sup>2</sup> found in the human being that a barium meal reached the stoma of an ileocolostomy between the fourth and sixth hours.

A significant observation was the consistency of retrograde filling of the proximal excluded colon (Figs. 6 and 7), which occurred uniformly

in all animals. The barium which entered at the site of anastomosis appeared to fill the proximal colon to the same extent and at the same rate as the distal colon. This has been frequently described in the human being.<sup>2</sup> The distal colon is evacuated first on defecation (Fig. 6), followed by a passage of the barium from the proximal into the distal colon. Retrograde filling of the cecum was quite common, although retrograde

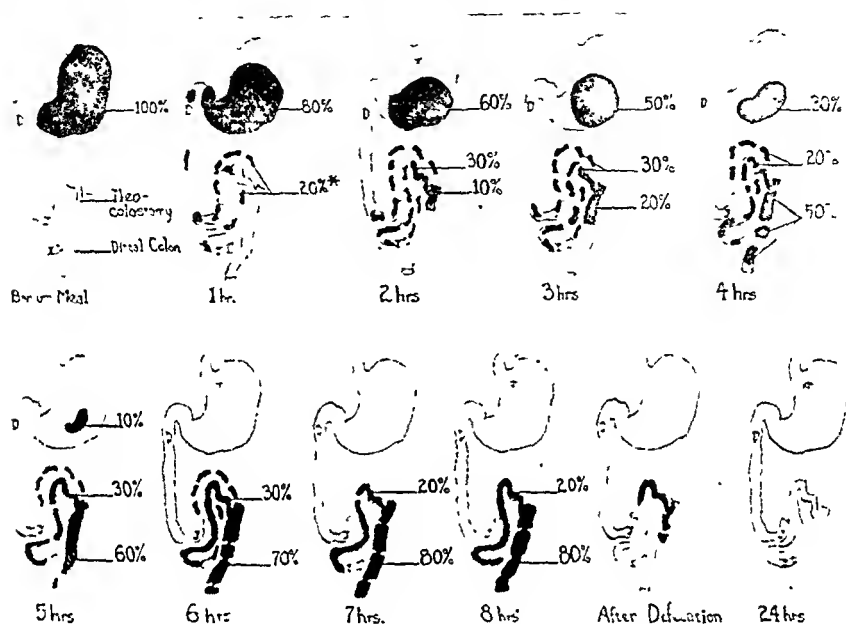


Fig. 5.—Record of average progress of motor meal in same series of dogs as represented in Figs. 3 and 4 following ileocolostomy and resection of proximal excluded colon, as drawn from fluoroscopy. Colonic filling began two and one-half to three hours earlier than in the normal control. Capacity of colon was limited so that partial evacuation of the colon occurred before the small intestine had emptied completely. The colon accommodated for limited capacity by temporary dilatation (see sixth to seventh hour record). Emptying time of the colon was the same as prior to surgery. Asterisk denotes percentage of barium in small intestine.

filling of the ileal stump was never seen. At the end of twenty-four hours the proximal excluded colon was invariably empty and the distal colon was usually empty, especially if defecation had been stimulated by feeding (Fig. 7). At no time did we observe impaction of the barium in the blind proximal colon, as reported to occur in the human being by Case.<sup>8</sup>

Ginzburg and his associates<sup>2</sup> found dilatation of the ileal loop adjacent to the anastomosis in one-third of their twenty-two patients, although evidence of ileal stasis was found in only two of them. We never observed dilatation of or stasis in the ileum adjacent to the anastomosis in the dog. This was confirmed by inspection at a subsequent operation (Fig. 8). However, we have seen temporary ileal dilatation following

partial colon resection; when the remaining colon had filled to capacity with barium, the remainder of the barium accumulated in the terminal portions of the ileum (Fig. 5) until the colon partially evacuated and could accommodate more barium. Gastric emptying time appeared to be shortened by one-half to one hour. Whether this is of significance is doubtful.



Fig 6—A. X-ray film following ileocolostomy. XX' marks site of anastomosis. Progress of barium meal at sixth hour. Note the degree of colonic filling at this time with retrograde filling of proximal excluded colon (P.C.) as far back as the cecum (C). B. Film of same animal two hours later, during which interval defecation had occurred. Note degree of emptying of proximal excluded colon (P.C.). At twenty-four hours entire colon had emptied.

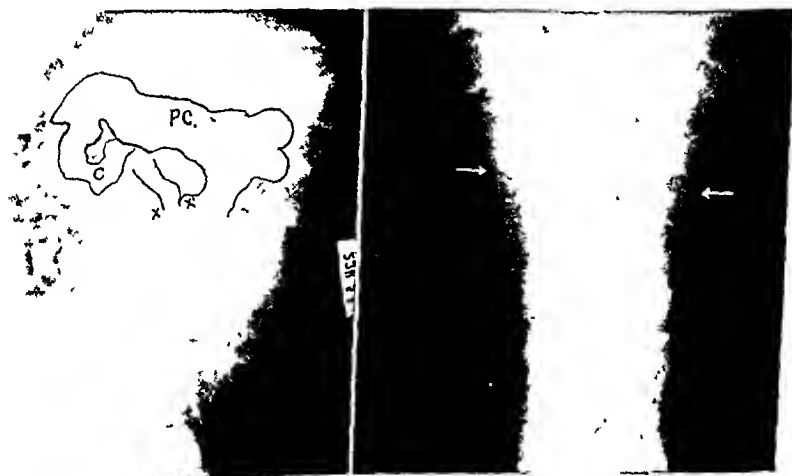


Fig 7.—A. X-ray film of pregnant dog following ileocolostomy. Margins of proximal excluded colon (P.C.) and anastomosis (XX') outlined with ink. Progress of barium at sixth hour. Note degree of colonic filling at this time with retrograde filling of proximal excluded colon (P.C.) as far back as the cecum (C). B. Film of same animal taken at twenty-four hour after defecation. Note complete evacuation of barium from all segments of the colon. Arrows point to fetuses which were delivered three weeks after the ileocolostomy.

Barium enemas usually revealed a simultaneous filling of the proximal colon and terminal ileum; whether the ileum or proximal colon filled first was variable, but the difference in time was slight. Dilatation of the terminal ileum was seen in none of the animals even with barium enema. Expulsion of the enema from all portions of the colon was usually as complete as prior to the ileocolostomy.



Fig. 8.—Photograph of ileocolostomy taken at time of resection of proximal excluded colon. Note that ileum (*I.*) is of normal caliber and that colon proximal to anastomosis (*P.C.*) is of about the same dimensions as distal colon (*D.C.*).

The clinical course of these animals postoperatively was satisfactory. During a four-month course no symptoms of bowel obstruction and no diarrhea or colitis occurred. The animals' appetites were excellent, the majority of them gaining 5 pounds or more in weight (10 to 15 per cent of total body weight).

The ileocolostomy was inspected at the subsequent resection of the proximal colon (Fig. 8). The anastomosis was usually covered by loosely adherent bands of omentum, which apparently contributed to its blood supply. The ileum was of normal dimensions and color and the stoma



permitted the insertion of the tip of the index finger from the colonic side. No evidence of dilatation or obstruction was present. The proximal excluded colon was of normal caliber and appeared the same in every respect as the distal colon. On inspection of the specimens of proximal colon following resection, they were seen to contain soft, formed fecal matter. The inverted ileal stump was well healed in all specimens, its lumen empty, and regurgitation into this structure appeared unlikely.

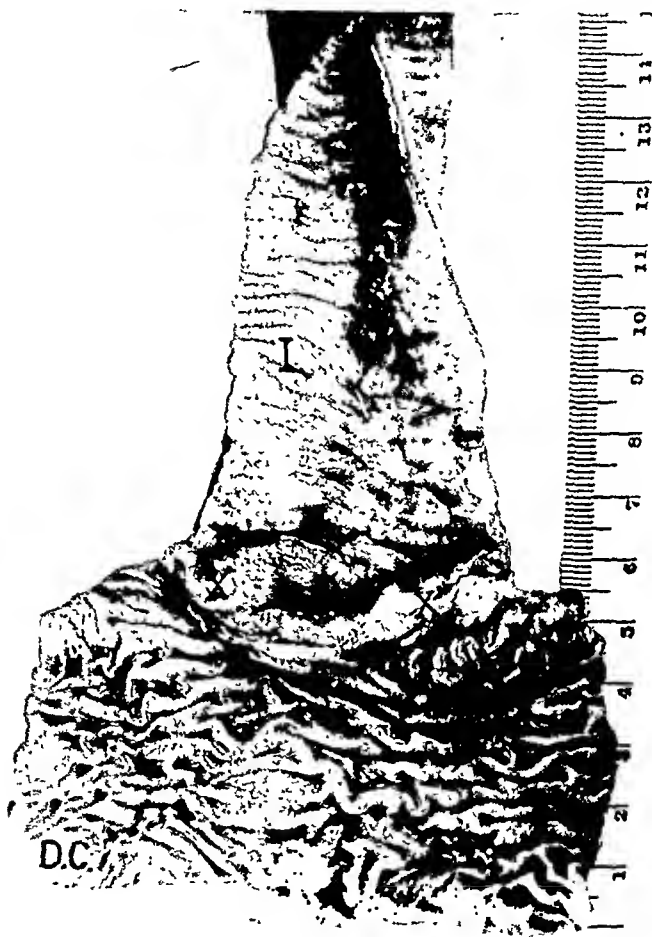


Fig. 9.—Photograph of fresh specimen of ileocolostomy from the same dog shown in Fig. 8; anastomosis removed three months after the resection of the proximal excluded colon. Note the ample stoma of the anastomosis XX' which is approximately 2.8 cm. in circumference. The mucosa of the ileum (I) and the distal colon (D.C.) appeared normal.

*Observations Following Partial Colon Resection.*—Resection of the colon proximal to the anastomosis was undertaken as a second-stage procedure following ileocolostomy. The segment removed included the inverted ileal stump, the cecum, ascending colon, transverse colon, and the upper portion of the descending colon. This was accomplished in all

nine dogs without a single mortality. The colon was removed as close to the anastomosis as possible to decrease the amount of blind colon left behind. The colon was sectioned transversely and inverted with a row of interrupted catgut sutures as described for the anastomosis. A second row of similarly applied silk sutures inverted the colon still more. The advantage of interrupted sutures for reliable closure was striking. In previous operations on dogs we had learned that the procedure of "open" anastomoses with the dog's colon was followed by a high mortality. The animals were treated postoperatively as they were after the ileocolostomy. The postoperative course of these animals was as uneventful as after ileocolostomy. None of the animals developed diarrhea, weight was maintained, and they appeared to be in good health.

A similar series of barium progress meal studies was made in the nine dogs and Fig. 5 is a composite representation of the average progress of the barium meals in all dogs following ileocolostomy and resection of the proximal excluded colon. Colonic filling was further shortened by one-half to one hour, a total shortening of two and one-half to three hours from the normal control observations. Gastric emptying time was about the same as after ileocolostomy, but emptying of the ileum appeared to be impeded by the limited capacity of the colon (Fig. 5, 8 hrs.). It usually required a defecation to evacuate the colon partially before the small intestine emptied completely. This appeared to have no permanent effect on the terminal ileum. The animals were capable of emptying their colons as completely after partial colon resection as before, and at the end of twenty-four hours the colon no longer contained any residual barium. Frequently we noted a compensatory dilatation of the distal colon (Fig. 5, 6 hrs.-7 hrs.)

#### DISCUSSION

That retrograde filling of the proximal excluded colon should have been an invariable accompaniment of the ileocolostomy is an item of considerable practical importance. Certainly the segment of the colon proximal to the anastomosis cannot be considered to be at physiologic rest. The fact that it evacuates synchronously with the distal colon, and that it contains dehydrated fecal matter, points further to its continued activity as under normal conditions. Whatever benefits are to be described as resulting from the procedure of ileocolostomy cannot be ascribed, we feel, to diversion of the fecal stream.

That colonic filling should commence two hours earlier following ileocolostomy, and still sooner after the resection of the proximal colon, appears to be due to the lack of a physiologic sphincter. Operative findings suggested anastomotic stomas far more patulous than the ilocecal sphincter. Obviously such rapid emptying of the small intestine is undesirable and efforts should be directed toward decreasing the speed of progress of the meal out of the small intestine. Barium enemas after

ileocolostomy further showed the patulous state of the new anastomosis. It is interesting to note that one of the arguments offered in favor of an end-to-side ileocolic anastomosis over the side-to-side technique was the preservation of the circular muscle fibers of the ileum and therefore a continued sphincter action at the stoma. Our observations do not support this contention.

We must not overlook the fact that our experimental procedure differs in two important aspects from the problem in the human being. First, we are dealing with the dog's colon which is shorter, smoother, and more tubular than the human colon. Second, our proximal excluded colon is essentially a normal one, whereas in the human being it is the site of some pathologic change. Whether the diseased proximal colon would evacuate its barium as rapidly as it did in our animals is another problem.

From our observations we feel that the chance of the blind loop of colon or inverted ileal stump developing pathologic changes due to its conversion into a blind loop is unlikely, for the colon can empty in the normal direction, and regurgitation into the ileal stump does not usually occur. Furthermore, neither of these two operative procedures interfered with the state of nutrition of the animals.

#### CONCLUSIONS

1. Ileocolostomy in the dog was followed by a two-hour decrease in the time of colonic filling. Following resection of the colon proximal to the anastomosis, this time was still further shortened.

2. Retrograde filling of the proximal excluded colon was an invariable accompaniment of ileocolostomy in dogs.

3. The proximal excluded colon cannot be assumed to be placed at physiologic rest as a result of ileocolostomy; nor does it appear to be likely to develop any pathologic changes as a result of the procedure.

4. Resection of the proximal one-half of the colon of the dog is frequently associated with temporary compensatory dilatation of the distal colon and temporary ileal stasis, apparently due to a limited colonic capacity.

5. The procedures of ileocolostomy and partial colonic resection in the dog can be accomplished without alteration of the nutrition and health of the animal.

We are obliged to Dr. Sidney Portis for suggestions and help, to Mr. Lamar Walker for technical assistance, and to Dr. Harold Laufman for drawing Figs. 1 and 2.

#### REFERENCES

1. Lewisohn, R.: Segmental Enteritis, *Surg. Gynec. & Obst.* 66: 215, 1938.
2. Ginzburg, L., Colp, R., and Sussman, R.: Ileostomy With Exclusion, *Ann. Surg.* 110: 648, 1939.
3. Berg, A. A.: An Operative Procedure for Right Sided Ulcerative Ileo-Colitis, *Ann. Surg.* 104: 1019, 1936.
4. Crohn, B. B.: Regional Ileitis, *Surg., Gynec. & Obst.* 68: 314, 1939.
5. Rankin, F. W., and Graham, A. S.: Aseptic End-to-Side Ileo-Colostomy: Clamp Method, *Ann. Surg.* 99: 676, 1934.

6. Lahey, F. H.: Resection of the Right Colon and Anastomosis of the Ileum to the Transverse Colon After the Plan of Mikulicz, *Surg., Gynec. & Obst.* 54: 923, 1932.
7. Rankin, F. W.: An Aseptic Method of Intestinal Anastomosis, *Surg., Gynec. & Obst.* 47: 78, 1928.
8. Case, J. T.: Roentgen Studies After Gastric and Intestinal Operations, *J. A. M. A.* 65: 1628, 1915.
9. Neuwelt, F., Medoff, J., Patedjl, J., and Necheles, H.: A Study of the Functions of the Stomach Following Pyloric Obstruction and Gastroenterostomy, *Am. J. Digest. Dis.* 8: 310, 1941.
10. Brown, L., and Sampson, H.: Intestinal Tuberculosis: Its Importance, Diagnosis, and Treatment, ed. 2, Philadelphia, 1930, Lea and Febiger, p. 55.
11. Wangensteen, O. H.: Aseptic Resections in the Gastro-Intestinal Tract, With Special Reference to Resection of the Stomach and Colon, *Surg., Gynec. & Obst.* 72: 257, 1941.

# THE PATHOGENICITY OF THE BACTERIA OF APPENDICITIS PERITONITIS

## AN EXPERIMENTAL STUDY

WILLIAM A. ALTEMEIER, M.D., CINCINNATI, OHIO

(From the Department of Surgery of the University of Cincinnati College of  
Medicine, and the Cincinnati General Hospital\*)

**P**ERITONITIS secondary to acute perforated appendicitis is rarely caused by a single type of bacterium. On the contrary, the bacterial flora of the peritonitis exudate is mixed and varied, and all of the intestinal bacteria may be found in the peritoneal exudate in such cases. In a previous study at the Henry Ford Hospital in 1938,<sup>1</sup> sixteen species of aerobic microorganisms and at least eighteen species of anaerobes were described in the purulent exudate taken from the immediate vicinity of the perforated appendix of 100 cases. Every exudate yielded at least one type of bacterium and in no instance was an entirely negative culture obtained. Three or more species of bacteria were recovered from 96 of the 100 cases and as many as seven types were occasionally isolated, similar to the findings of Weinberg, Prevot, Davesne, and Renard in 1928.<sup>2</sup> The average number of anaerobic species in a case often exceeded that of the aerobic, agreeing with the previous reports of Veillon and Zuber,<sup>3</sup> Runneberg,<sup>4</sup> and Heyde.<sup>5</sup> Among the aerobes recovered were *Bacillus coli*, streptococci, *B. pseudodiphtheriae*, staphylococci, *B. lactis aerogenes*, *B. proteus*, *B. alkaligenes*, *B. subtilis*, and *B. mesentericus*; and among the anaerobes were *B. melanogenicum*, streptococci, gram-negative diplococci, *B. thetoides*, *B. fragilis*, and members of the Clostridium group.

In this paper the pathogenicity of these bacteria in pure and mixed culture has been studied. The aerobic organisms were cultivated for twenty-four hours in beef extract broth or brain broth. Two cubic centimeters of this material were then injected subcutaneously and intraperitoneally into guinea pigs and the results are shown in Fig. 1. By using liquid media it was thought the results obtained would represent not only the virulence of the bacteria themselves but also the toxicity of their accumulated metabolic products. The majority of the strains tested produced minor local lesions or cellulitis about the point of subcutaneous inoculation, but usually failed to cause a fatal peritonitis. The aerobes capable of producing a fatal peritonitis included some strains of *B. coli*, *B. pyocyaneus*, and *B. alkaligenes*. Twenty-one strains of *B. coli* were thus tested and three of these were quite virulent, producing large areas

\*The greater part of this work was done at the Henry Ford Hospital, Detroit, Mich.  
Received for publication, June 14, 1941.

of cellulitis and rapidly fatal peritonitis. The low virulence of the remaining eighteen was quite surprising. The nonhemolytic aerobic streptococcus, which usually presented the cultural characteristics of the *Streptococcus faecalis*, was found to have little or no virulence.



Fig. 1—Results of the injection of pure cultures of bacteria subcutaneously in a guinea pig (see Table III, Case 2). 1. *B. coli* 2. Aerobic streptococcus. 3. *B. pyocyaneus* 4. *B. melanogenum*. 5. Anaerobic coccus. Note the very minor lesions produced

The virulence of these aerobic bacteria, particularly *B. coli*, for guinea pigs and rabbits could be greatly increased by the coincidental injection through a large bore needle of many particles of autoclaved sterile tissue. For example, if an avirulent culture of *B. coli* was injected along with many fine pieces of autoclaved brain or muscle tissue, cellulitis and fatal peritonitis invariably occurred. Similar observations have been made previously. Halsted,<sup>6</sup> working with *Staphylococcus aureus*, found that dogs did not develop peritonitis when a bouillon culture of the bacterium was introduced into the peritoneal cavity. However, if a small piece of potato was introduced along with the bacteria, a fatal peritonitis de-

veloped. Similarly, if a small piece of omentum was tied off and strangulated within the abdominal cavity, its contamination with staphylococci frequently resulted in peritonitis.

Many of the anaerobic organisms were difficult to cultivate in pure culture. By using deep tubes containing brain broth and a small amount of blood, a fairly good growth was usually obtained under strict anaerobic conditions. In the case of the anaerobes, 2 c.c. of a forty-eight- or seventy-two-hour culture were usually used for the inoculations. The



Fig. 2.—Extensive cellulitis and gangrene produced by the subcutaneous inoculation of a mixed culture of the same bacteria used in Fig. 1. *B. coli*, aerobic streptococcus, *B. pyocyaneus*, *B. melaninogenicum*, and anaerobic coccus (see Table III, Case 2).

majority of the anaerobic bacteria investigated did not produce a fatal peritonitis, with the exception of hemolytic streptococci, *B. thetoides*, and *B. fragilis*. The anaerobic *B. melaninogenicum* frequently found in our series of peritonitis exudates was separated with great difficulty from a nonhemolytic streptococcus with which it was frequently and intimately associated. Both were found to be relatively nonpathogenic.

A study of Tables I and II shows that the majority of bacteria found in appendicitis peritonitis, when injected in pure culture, did not produce a fatal peritonitis. If, however, several or more strains of these bacteria found in a given case of peritonitis were mixed and cultivated simulating their existence in the peritonitis exudate, their composite virulence was greatly increased. The synergistic effect produced by these bacteria was repeatedly demonstrated. The various strains of bacteria

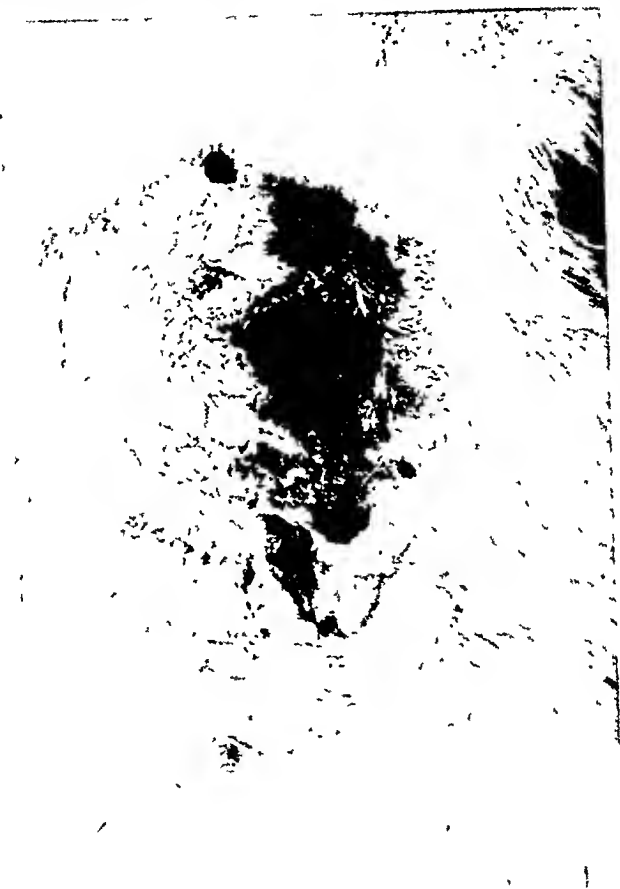


Fig. 3.—Cutaneous gangrene in the guinea pig produced by the subcutaneous injection of a mixed culture of *B. coli*, nonhemolytic streptococcus, anaerobic coccobacillus, anaerobic coccus (large), and anaerobic micrococcus (see Table III, Case 1)

isolated from a given case of appendicitis peritonitis were inoculated in pure culture subcutaneously and intraperitoneally into laboratory animals and their effect noted. Subcutaneously, relatively minor lesions usually were the result. (Table III and Fig. 1) Intraperitoneally the great majority of these bacteria did not produce a fatal peritonitis in the dosages employed. When the same strains of organisms were mixed, cultivated, and then injected into similar experimental animals, it was



TABLE I  
PATHOGENICITY OF ANAEROBIC BACTERIA IN PURE CULTURE FOR GUINEA PIGS

ANAEROBIC BACTERIA	NO OF STRAINS	SUBCUTANEOUS INOCULATION	INTRAPERITONEAL INJECTION
1 <i>B. coli</i>	18	Negative, slight local reaction, cellulitis	Survived
2. Streptococcus, nonhemolytic	3	which may produce cutaneous gangrene	Fatal peritonitis
3 <i>B. pseudodiphtheriae</i>	9	Negative, or small area of induration	Survived
4 Streptococcus, green producing	3	Small area of cellulitis	Survived
5 Streptococcus, hemolytic	2	Cellulitis with small area of central gangrene, localized abscess with surrounding area of cellulitis	Listless, survived
6 <i>B. pyovivans</i>	2		Survived
7 <i>Staph aureus</i>	3	Diffuse cellulitis	Dead in less than 20 hr.
8 <i>B. lactis aerogenes</i>	2	Localized abscess	Survived
9. <i>B. proteus</i>	2	Localized induration	Survived
10 <i>B. albidogenes</i>	2	Negative, or local induration	Survived
11. <i>B. subtilis</i>	2	Negative	Animals dead in 36-48 hr
12 <i>B. mesentericus</i>	2	Negative	Survived

TABLE II  
PATHOGENICITY OF ANAEROBIC BACTERIA IN PURE CULTURE FOR GUINEA PIGS

ANAEROBIC BACTERIA	NO OF STRAINS	SUBCUTANEOUS (2 cc)	INTRAPERITONEAL (2 cc)
1 <i>B. melanogenium</i>	3	Induration with small crepitant abscess in some instances	Survived
2 Streptococcus, nonhemolytic	4	Negative, local induration, local abscess	Survived
3 Streptococcus, hemolytic	5		Survived
4 <i>B. thiodetes</i>	2	Local abscess	Death in 24 hr.
5 Staphylococcus	2	Cellulitis with death of animals	Death in 24 hr.
6 <i>B. frautis</i>	2	Local abscess	Survived
7 Streptobacterium	1	Local abscess followed by death	Death in 72 hr
8 <i>B. pseudodiphtheriae</i>	1	Local abscess	Death in 24 hr
9 <i>Cl. aerofaciens</i>	3	Negative	Survived
10. <i>Cl. sporogenes</i>	1	Cellulitis, animals survived	Survived
11. <i>Cl. fallax</i>	1	Local inflammation	Survived
12 Gram + streptobacillus	1	Crepitant cellulitis	Survived
13 <i>Cl. uelchu</i>	2	Negative	Survived
		Cellulitis, ulceration, and gangrene	Survived

found that an equal or smaller dose resulted in extensive areas of cellulitis frequently accompanied by gangrene (Figs 2, 3, and 4; Table III) and frequently overwhelmingly fatal peritonitis.

These facts combined with the observation that many of these bacteria grow sparsely in pure culture, but profusely in mixed culture, suggest that they exist in the peritonitis exudates in a state of symbiosis and that their synergistic effect plays a large part in the infection.



Fig 1—Gangrene following subcutaneous injection of mixed culture of *B. lactis aerogenes*, *E. pseudodiphtheriae*, nonhemolytic streptococcus, *B. melanogenicum*, anaerobic micrococcus and *Cl. acetofaciens* (see Table III, Case 5).

#### DISCUSSION

There are many reasons why it is difficult to estimate the human pathogenic power of the bacteria associated with appendicitis peritonitis. Not only are there many different species of bacteria found in the peritonitis exudate, but considerable variation in virulence also occurs among different strains of the same species. Many of the bacteria probably lose their pathogenic power under the repeated sub-

PATHOGENICITY OF ANAEROBIC BACTERIA IN PURE CULTURE FOR GUINEA PIGS

ANAEROBIC BACTERIA	NO OF STRAINS	SUBCUTANEOUS INOCULATION	INTRAPERITONEAL INJECTION
1 <i>B. coli</i>	19	Negative, slight local reaction, cellulitis which may produce cutaneous gangrene	Survived
2. Streptococcus, nonhemolytic	3	Negative, or small area of induration	Fatal peritonitis
3 <i>B. pseudodiphtheriae</i>	9	Small area of cellulitis	Survived
4 Streptococcus, green producing	3	Cellulitis with small area of central gangrene, localized abscess with surrounding area of cellulitis	Survived
5 Streptococcus, hemolytic	2	Diffuse cellulitis	Listless, survived
6 <i>B. pyogenes</i>	3	Localized abscess	Survived
7. <i>Staph. aureus</i>	2	Localized induration	Dead in less than 20 hr.
8. <i>B. lactis aerogenes</i>	2	Negative, or local induration	Survived
9. <i>B. proteus</i>	2	Negative	Survived
10. <i>B. alkaligenes</i>	2	Negative	Animals dead in 36-48 hr
11. <i>B. subtilis</i>	2	Negative	Survived
12 <i>B. mesentericus</i>	2	Negative	Survived

TABLE II

PATHOGENICITY OF ANAEROBIC BACTERIA IN PURE CULTURE FOR GUINEA PIGS

ANAEROBIC BACTERIA	NO OF STRAINS	SUBCUTANEOUS (2 C.C.)	INTRAPERITONEAL (2 C.C.)
1 <i>B. melaninogenicum</i>	3	Induration with small crepitant abscess in some instances	Survived
2 Streptococcus, nonhemolytic	4	Negative; local induration; local abscess	Survived
3 Streptococcus, hemolytic	3	Local abscess	Survived
4 <i>B. thurbergs</i>	2	Cellulitis with death of animals	Death in 24 hr
5 <i>Staphylococcus</i>	2	Local abscess	Death in 24 hr.
6 <i>B. fragilis</i>	2	Local abscess followed by death	Survived
7 Streptobacterium	1	Negative	Death in 72 hr
8 <i>B. pseudodiphtheriae</i>	1	Cellulitis, animals survived	Survived
9 <i>C. aerofaciens</i>	3	Local inflammation	Survived
10 <i>C. fallax</i>	1	Crepitant cellulitis	Survived
11 <i>C. parvulus</i>	1	Negative	Survived
12 Gram + streptococcus	1	Cellulitis, ulceration, and gangrene	Survived
13 <i>C. urethrae</i>	2		Survived

cultivations necessary for their isolation in pure culture and their proper identification, and this may have occurred in our experiments. The laboratory animals used to test virulence may have a susceptibility entirely different from the human being and may actually possess either a natural individual or species immunity. Evidence is accumulating that some bacteria such as the anaerobic streptococci are definitely pathogenic for human beings under certain conditions, yet all attempts to demonstrate their pathogenicity in experimental animals have failed. Finally, metabolic diseases, individual human variations in general health, and susceptibility to infection are all factors of importance which determine the pathogenic power of bacteria in an individual case.

In the experiments presented in this paper there is strong evidence that the accumulative action of all the bacteria, aerobic and anaerobic, determine to a large extent the nature and severity of the peritoneal infection. It appears that slightly or apparently nonpathogenic microorganisms may play an important part in the course of the peritonitis by increasing the virulence of the bacteria with which they are associated.

Symbiosis in disease has attracted relatively little attention in medicine and surgery. The course of medical investigation and reasoning since the time of Pasteur, and more particularly Koch, has been toward the monoetiology of disease. Indeed, the fulfillment of Koch's postulates is generally required for the establishment of the etiology of a disease. Largely for this reason the true nature of many pathologic processes has remained obscure.

The biologic relations of microorganisms are of the greatest significance in the economy of nature and in the production of disease (Kendall<sup>7</sup>). Bacteria in nature do not grow in pure culture, although in the tissues of man or animals they may do so as disease-producing bacteria. One of the important functions of bacteria is to reduce dead organic matter into mineralized salts, the successive steps being effected by different species of microbes. Frequently the products of such symbiotic activity are greater than the total of the separate activities of the bacteria. In man and animals, natural infection with more than one bacterium is relatively frequent, and the particular combinations which may occur to a large extent determine the course of the disease. Rogers<sup>8</sup> (1889) was the first to show that *B. prodigiosus* added to the bacillus of malignant edema made sublethal injections of this anaerobe fatal for rabbits. Novy<sup>9</sup> found association of *B. proteus* and *B. oedematis* produced rapid death of guinea pigs. Barrien<sup>10</sup> (1920) noted that *B. proteus* and nonpathogenic spore-bearing aerobes in wounds exhibited the virulence of pathogenic bacteria. Kammerer<sup>11</sup> introduced the term "synergism" into bacteriologic nomenclature to indicate the sum activity of two or more microorganisms. He cited examples of synergistic action in observations on the reduction of pure bilirubin and mesobilirubin to urobilin by emulsions of human feces. The syner-

BACTERIA ISOLATED	PATHOGENICITY IN PURE CULTURES FOR GUINEA PIGS			PATHOGENICITY IN MIXED CULTURES FOR GUINEA PIGS		
	SUBCUTANEOUS (2 C.C.)		INTRAPERITONEAL (2 C.C.)	SUBCUTANEOUS (2 C.C.)		INTRAPERITONEAL (2 C.C.)
	Negative	Negative	Survived	Extensive cellulitis in center of which gangrene usually occurred	Extensive cellulitis with gangrene	Animals dead in 12-24 hr.
Case 1. <i>B. coli</i> Nonhemolytic streptococcus (aerobic) Gram + coccobacillus (anaerobic) Anaerobic coccus Anaerobic microstreptococcus	Local induration	Local abscess	Survived	Survived	Animals dead in 18-36 hr.	
Case 2. <i>B. coli</i> Nonhemolytic streptococcus <i>B. pyocyaneus</i> <i>B. melanogenicum</i> Anaerobic coccus	Local induration	Local abscess	Survived	Survived	Animals dead in 12-24 hr.	
Case 3. <i>B. coli</i> <i>Staph. aureus</i> <i>B. melanogenicum</i> Anaerobic streptococcus	Local abscess	Local abscess	Survived	Survived	Animals dead in 5-8 days	
Case 4. <i>B. coli</i> Nonhemolytic streptococcus (aerobic) <i>B. melanogenicum</i> Anaerobic micrococcus <i>B. fragilis</i>	Local cellulitis	Induration with small abscess	Survived	Extensive hemorrhagic cellulitis with death of animals in 48-72 hr.	Animals dead in 24-48 hr.	
Case 5. <i>B. lactis aerogenes</i> <i>B. pseudodiphtheriae</i> Nonhemolytic streptococcus <i>B. melanogenicum</i> Anaerobic micrococcus <i>Cl. aerofaciens</i>	Local abscesses; death in 4 days	Induration with small abscess	Survived	Extensive cellulitis with gangrene and ulceration; animals survived	Animals dead in less than 24 hr.	
Case 6. <i>B. coli</i> <i>B. pseudodiphtheriae</i> Nonhemolytic streptococcus <i>B. pyocyaneus</i> <i>Staph. albus hemolyticus</i>	Local abscess	Large area of cellulitis	Survived	Large area of cellulitis with central gangrenous slough and ulceration	Animals survived	

effects, nor any abnormality in the peritoneal cavity beyond slight injection. However, by adding gum tragacanth to the *B. coli* suspensions, he was able to produce death by intraperitoneal injection in rabbits within thirteen to thirty-six hours. Steinberg<sup>19</sup> cited the frequent inability of investigators to produce a fatal peritonitis experimentally by intraperitoneal injections of saline suspensions of *B. coli*, and he adopted the method of Benians of inoculating *B. coli* suspended in gum tragacanth.

In summary, an analysis of the literature and of our experiments indicates that appendicitis peritonitis is usually a "polymicrobial" infection caused by the synergistic pathogenic action of a group of bacteria existing in the peritonitis exudate in a state of symbiosis. Correlation of clinical and experimental studies shows that the greater the number of bacterial species present within the exudate, the greater the severity of the peritoneal infection is likely to be.

#### CONCLUSIONS

1. The pathogenicity of the aerobic and anaerobic bacteria most frequently isolated from the peritoneal exudate of 100 cases of acute perforated appendicitis was studied in experimental animals.

2. The great majority of these bacteria did not produce a fatal peritonitis when injected in pure culture.

3. The ascription of acute perforated appendicitis peritonitis to the unaided activity of *B. coli* or other single strains of bacteria seems without sufficient justification in the average case.

4. Many avirulent strains of bacteria, particularly *B. coli*, become highly virulent in the presence of dead sterile tissue within the peritoneal cavity.

5. In mixed culture these bacteria show a synergistic action producing a high degree of pathogenicity.

6. Acute perforated appendicitis peritonitis appears to be an infection resulting from the synergistic activities of the various bacterial symbionts present in a given case.

#### REFERENCES

1. Altemeier, W. A.: Bacterial Flora of Acute Perforated Appendicitis With Peritonitis; Bacteriologic Study Based on 100 Cases, *Ann. Surg.* 107: 517-528, 1938.
2. Weinberg, M., Prevot, A. R., Davesne, J., and Renard, C.: Recherches sur la bacteriologie et la serotherapie des appendicites aigues, *Ann. Inst. Pasteur* 42: 1167-1241, 1928.
3. Veillon, A., and Zuber, A.: Recherches sur quelques microbes strictement anaerobes et leur role en pathologie, *Arch. de med. exper. et d'anat. path. par.* 10: 517, 1898.
4. Runenberg, B.: Studien über die bei peritonealen Infektionen appendikulären Ursprungs vorkommenden Sauerstofftoleranten, mit besonderer Berücksichtigung ihrer Bedeutung für die Pathogenese derartiger Peritonitiden, *Arch. n.d. Path. Inst. d. Univ. Helsinki* 1: 271, 1905.
5. Heyde, M.: Bakteriologische und experimentelle Untersuchungen zur Ätiologie der Wurmfortsatzentzündungen (mit besondere Berücksichtigung der anaero-

gistic activity of *B. putrificus* and certain aerobes he believed was responsible for this. Roux and Yersin<sup>8</sup> restored the virulence of an avirulent strain of *B. diphtheriae* by the addition of a nonfatal dose of the streptococcus of erysipelas. Jacobson,<sup>13</sup> Wolf,<sup>10</sup> Albert and Kilman,<sup>11</sup> Roos,<sup>12</sup> and Hudson<sup>13</sup> all found that the virulence of *B. influenzae* was increased when mixed with streptococci. Coley<sup>14</sup> showed the streptococcus was more virulent in combination with the *B. prodigiosus*. Jennings<sup>15</sup> (1923) discussed the role of *Cl. welchii* in appendicitis, and he believed that *Cl. welchii* infection occurred as a rule in symbiosis with a number of other bacteria.

Weinberg, Prevot, Davesne, and Renard (1928)<sup>2</sup> found anaerobes predominant in purulent exudates of gangrenous appendicitis. Their experiments suggested the possibility that not only appendicitis but also peritonitis was the result of the combined action of bacterial mixtures.

Mcleney, Olpp, Harvey, and Jenn<sup>16</sup> (1932) observed that if more than one type of intestinal bacterium was present in the peritoneal exudate, the clinical course of the illness was much more serious than when only one was present. They studied the pathogenicity of *B. coli*, non-hemolytic streptococci, and *Cl. welchii* which were the organisms commonly found by them in peritonitis. All four possible combinations of these three species were made. When any two or all three types were combined, the mixture was lethal in quantities considerably less than the lethal doses in pure culture. This work clearly shows the synergistic activity of these three symbionts in peritonitis. In our experiments a similar cumulative action of many more species of bacteria, both aerobic and anaerobic, in peritonitis has been shown.

The symbiotic existence of the intestinal bacteria within the intestinal tract is generally recognized. Experimental evidence indicates that the same bacteria exist in a similar state in the peritoneal exudates of perforated appendicitis. The synergistic pathogenic effect of the different strains of bacteria growing in symbiosis has been demonstrated by our experiments. These experiments also substantiate our previous observation<sup>1</sup> that the more clinically severe cases of appendicitis peritonitis occurred most frequently when five or more species of bacteria were present in the exudate. No case died in which only one species of bacterium was found.

As noted previously the low virulence of the majority of strains of *B. coli* isolated by us was unexpected and surprising. Jordon<sup>17</sup> regarded the pathogenicity assigned to *B. coli* by some investigators, notable French bacteriologists, to be greatly exaggerated. He regarded the frequent ascription of various inflammatory processes, particularly those occurring in the appendix and peritoneum, to the unaided activities of *B. coli* to be without sufficient justification. Benians<sup>18</sup> was able to inject intraperitoneally 2500 million living *B. coli* from a twenty-four-hour culture in saline suspensions into rabbits with no obvious ill

# PEPTIC ULCER IN MECKEL'S DIVERTICULUM CAUSING INTRINSIC INTESTINAL OBSTRUCTION

## REPORT OF TWO CASES

JOHN M. WAUGH, M.D., WALLACE E. HERRELL, M.D., AND  
LEO K. CRUMPACKER, M.D.,\* ROCHESTER, MINN.

*(From the Divisions of Surgery and Medicine, the Mayo Clinic, and the Mayo Foundation)*

MECKEL'S diverticulum is a congenital anomaly which occurs in about 1 to 2 per cent of all persons. The mucous membrane of the diverticulum usually is of the ileal type, but may be gastric and, less often, duodenal, jejunal, pancreatic, or colonic. Schaetz<sup>1</sup> found gastric mucosa in 16 per cent of his specimens, Carlson<sup>2</sup> and Bussey<sup>3</sup> in 15 per cent of specimens removed surgically at the Mayo Clinic. Hudson and Koplik<sup>4</sup> found that 52 per cent of their specimens, which were the sites of acute lesions, contained gastric mucosa. This may indicate that the presence of gastric mucosa is more likely to be associated with pathologic change than is the presence of ileal mucosa.

Halstead<sup>5</sup> in 1902 reviewed 69 cases of intestinal obstruction secondary to Meckel's diverticulum, and Deetz<sup>6</sup> in 1907 reported on an acute perforation at the base of a Meckel's diverticulum in a boy 9 years old. The clinical picture of peptic ulceration of Meckel's diverticulum, however, is relatively new. Cobb,<sup>7</sup> in 1936, analyzed 100 cases of probable peptic ulcer in Meckel's diverticulum, most of which had been reported in the literature since 1924. In 66 cases gastric mucosa was found in the diverticulum on microscopic examination. In the remaining cases it either was not found or was not mentioned. Seventy-four per cent of the patients were 15 years of age or less. Eighty-one ulcers afflicted men, 14 afflicted women, and in 5 instances the sex of the patients was not stated. The ratio of the incidence of Meckel's diverticulum among men to that among women was 2:1. Eighty per cent of the patients had abdominal pain of some type. The most frequent complication, bleeding from the rectum, occurred in 72 per cent of the cases. Perforation was found in 55 per cent of the cases, either at the time of operation or on post-mortem examination.

Two features repeatedly mentioned by most investigators of the subject under consideration is that the lesion is situated in the region of ordinary intestinal mucosa close to the boundary of the heterotopic gastric mucosa of fundic type and that, usually, a single ulcer is present. When the entire pouch of the diverticulum is lined with gastric mucosa, the ulcer is situated in the ileum close to the neck of the Meckel's

\*Fellow in Surgery, the Mayo Foundation.  
Received for publication, June 16, 1941.



6. Halsted, W. S.: Inoculations of the Peritoneal Cavity With Pure Culture of the *Staphylococcus Aureus*, Johns Hopkins Hosp. Rep. 2: 255, 1891.
7. Kendall, A. I.: Intestinal Bacteriology: A Summary, J. A. M. A. 56: 1084-1088, 1911.
8. Holman, W. L.: Bacterial Association, in Jordan and Falk: The Newer Knowledge of Bacteriology and Immunology, Chicago, 1928, University of Chicago Press, chap. 8, pp. 102-119.
9. Kammerer, H.: Ueber Porphyrinbildung durch Darmbakterien, Klin. Wchnschr. 2: 1153-1155, 1923.
10. Wolf, J. E.: Beitrage zur Biologie des Pfeifferesche Influenzabacillus, Mischkulturen, Mischinfektion, Centralbl. f. Bakt. 84: 241-256, 1920.
11. Albert, H., and Kilman, S.: The Pathogenicity of *Bacillus influenzae* for Laboratory Animals, J. Infect. Dis. 25: 433-443, 1919.
12. Roos, C.: Notes on the Bacteriology and on the Selective Action of *B. Influenzae Pfeiffer*, J. Immunol. 4: 189-201, 1919.
13. Hudson, N. P.: Inoculation of White Mice With Pfeiffers Bacillus, J. Infect. Dis. 30: 433-442, 1922.
14. Coley: Quoted by McFarland, J.: Pathogenic Bacteria and Protozoa, ed. 9, Philadelphia, 1919, W. B. Saunders Co., p. 57.
15. Jennings, J. E.: Role of *Bacillus Welchii* in Gangrenous Appendicitis, and Use of Antitoxin of Bull and Prichett in Its Treatment, New York M. J. 117: 682, 1923.
16. Meleney, F., Olpp, S., Harvey, H. D., and Jenn, H.: Peritonitis. II. Synergism of Bacteria Commonly Found in Peritoneal Exudates, Arch. Surg. 25: 709, 1932.
17. Jordon, E. O., General Bacteriology, ed. 9, Philadelphia, 1928, W. B. Saunders Co., p. 311.
18. Benians, T. H. C.: Further Experiments With Fixation Areas, Bearing on Pathogenicity of *Bacillus Coli* in Peritoneal Infections, Brit. J. Exper. Path. 5: 123, 1924.
19. Steinberg, B.: Cause of Death in Acute Diffuse Peritonitis, Arch. Surg. 23: 145, 1931.

# PEPTIC ULCER IN MECKEL'S DIVERTICULUM CAUSING INTRINSIC INTESTINAL OBSTRUCTION

## REPORT OF TWO CASES

JOHN M. WAUGH, M.D., WALLACE E. HERRELL, M.D., AND  
LEO K. CRUMPACKER, M.D.,\* ROCHESTER, MINN.

*(From the Divisions of Surgery and Medicine, the Mayo Clinic, and the Mayo Foundation)*

MECKEL'S diverticulum is a congenital anomaly which occurs in about 1 to 2 per cent of all persons. The mucous membrane of the diverticulum usually is of the ileal type, but may be gastric and, less often, duodenal, jejunal, pancreatic, or colonic. Schaetz<sup>1</sup> found gastric mucosa in 16 per cent of his specimens, Carlson<sup>2</sup> and Bussey<sup>3</sup> in 15 per cent of specimens removed surgically at the Mayo Clinic. Hudson and Koplik<sup>4</sup> found that 52 per cent of their specimens, which were the sites of acute lesions, contained gastric mucosa. This may indicate that the presence of gastric mucosa is more likely to be associated with pathologic change than is the presence of ileal mucosa.

Halstead<sup>5</sup> in 1902 reviewed 69 cases of intestinal obstruction secondary to Meckel's diverticulum, and Deetz<sup>6</sup> in 1907 reported on an acute perforation at the base of a Meckel's diverticulum in a boy 9 years old. The clinical picture of peptic ulceration of Meckel's diverticulum, however, is relatively new. Cobb,<sup>7</sup> in 1936, analyzed 100 cases of probable peptic ulcer in Meckel's diverticulum, most of which had been reported in the literature since 1924. In 66 cases gastric mucosa was found in the diverticulum on microscopic examination. In the remaining cases it either was not found or was not mentioned. Seventy-four per cent of the patients were 15 years of age or less. Eighty-one ulcers afflicted men, 14 afflicted women, and in 5 instances the sex of the patients was not stated. The ratio of the incidence of Meckel's diverticulum among men to that among women was 2:1. Eighty per cent of the patients had abdominal pain of some type. The most frequent complication, bleeding from the rectum, occurred in 72 per cent of the cases. Perforation was found in 55 per cent of the cases, either at the time of operation or on post-mortem examination.

Two features repeatedly mentioned by most investigators of the subject under consideration is that the lesion is situated in the region of ordinary intestinal mucosa close to the boundary of the heterotopic gastric mucosa of fundic type and that, usually, a single ulcer is present. When the entire pouch of the diverticulum is lined with gastric mucosa, the ulcer is situated in the ileum close to the neck of the Meckel's

\*Fellow in Surgery, the Mayo Foundation  
Received for publication, June 16, 1941.

diverticulum. The macroscopic and microscopic pictures resemble those of typical, chronic gastric and duodenal ulcers.

Analysis of secretion of the heterotopic gastric mucous membrane obtained from an open umbilical fistula by Tillmanns, Lexer, Denneé, Rosthorn, Stone, and A. L. Taylor<sup>6</sup> proved that it contained both pepsin and hydrochloric acid. Lindau and Wulff<sup>9</sup> expressed the belief that the occurrence of ulcers in Meckel's diverticulum lends support to the theory of the biochemical origin of peptic ulcer.

As previously stated, most of these ulcers produced either bleeding or some type of abdominal pain, with or without symptoms and signs of peritonitis caused by perforation. In the cases which are to be presented herein the scarring of the chronic peptic ulcers had, however, so narrowed the ileum that partial obstruction had occurred, and we believe it was this partial obstruction which was causing the recurrent abdominal pain associated with vomiting in the first case and the colicky pain in the second.

On the basis of study of the cases reported by Halstead and Cobb and a review of the cases which have appeared in the literature, we have been unable to find any instance in which a peptic ulcer in a Meckel's diverticulum caused scarring and resultant intrinsic partial or complete intestinal obstruction. Reported cases in which the condition has been associated with intestinal obstruction have shown that such obstruction was of the extrinsic type. Brown and Pemberton<sup>10</sup> reported 2 cases in which an ileac ulcer was situated at the mouth of a Meckel's diverticulum. In both cases gross and occult blood was found in the stools and in both there were annular lesions causing obstruction which apparently were similar to the lesion in our cases. Brown and Pemberton thought the Meckel's diverticula in their 2 cases were incidental and chose to call the ulcers "solitary ulcer of the ileum" because the Meckel's diverticula contained ileac mucosa and because there was no evidence of gastric mucosa. Cobb, as well as Brown and Pemberton, has called attention to the presence of an ulcer in or near a Meckel's diverticulum in which no gastric mucosa was demonstrable, and also to the absence of such ulceration in certain cases in which gastric mucosa was present. The former condition is difficult to explain, but the latter is no more so than is the explanation of the absence of peptic ulcer in the duodenum of most persons.

#### REPORT OF CASES

CASE 1.—The patient, a married woman, 22 years old, registered at the Mayo Clinic on Sept. 4, 1938, complaining of abdominal cramps of ten years' duration. In 1928, at the age of 12 years, she had had occasional attacks of cramplike pain across the lower part of the abdomen, which extended into both lumbar regions, and she stated that the left leg became stiff with each attack. Sometimes these attacks were associated with nausea and vomiting. In 1933, in the course of an exploratory operation performed elsewhere, the appendix had been removed, but the patient was told that the appendix was not the cause of her condition.

In 1935 attacks had occurred about once a month; fecal vomiting had been associated with one attack. These attacks had persisted, and in 1937 another exploratory operation had been performed, but nothing abnormal had been found.

The patient had consulted many physicians. Her condition had been diagnosed as "colitis," "adhesions" and "functional colon." The disability had progressed, however, so that at the time of the patient's admission to the Clinic she was experiencing almost constant abdominal pain which could be relieved only by the hypodermic injection of morphine sulfate. For many years she had taken laxative agents frequently to relieve constipation. There was no history of bloody or tarry stools. Menses, which had begun when the patient was 13 years of age, had been regular until June, 1938, and since that time had been eight to ten days late.

On physical examination at the clinic the patient appeared to be constitutionally inferior. The abdomen was not distended, but pelvic examination revealed that the left Fallopian tube and ovary were slightly enlarged and tender.

Results of routine laboratory examinations, consisting of urinalysis, leucocyte counts, determination of sedimentation rate and of blood urea, study of smears of the blood and a flocculation test, were normal or within the range of normal. The value for hemoglobin was 10 Gm. per 100 cc of blood; erythrocytes numbered 4,040,000 per cubic millimeter; and roentgenograms of the thorax revealed nothing abnormal.

An exploratory operation was advised, but no assurance of relief was given. Accordingly, on Sept. 7, 1938, the abdomen was opened by one of us (J. M. W.) through a low midline incision. A hydrosalpinx of the left tube was found and left salpingectomy was performed. This lesion was not felt to be the source of the trouble, however. On further exploration a Meckel's diverticulum was found about 60 cm. (2 feet) from the ileocecal valve, which measured 5 cm. in diameter and was greatly thickened and hypertrophied. The lumen of the small intestine above the diverticulum was dilated to about two times normal size and the wall was thickened and hypertrophied. Below the diverticulum the small intestine was collapsed. At the junction of the distal portion of the ileum with the diverticulum a chronic penetrating type of ulcer was encountered. The lumen of the intestine at this point would not admit the tip of the gloved fifth finger. The diverticulum and the adjacent portion of the small bowel were removed. Intestinal continuity was reestablished by closure of both ends and the making of a side to side anastomosis. A Witzel type of enterostomy was performed above the anastomosis as a safety measure. The enterostomy tube was brought to the outside through a stab wound in the right lower quadrant of the abdomen.

The patient made an uneventful convalescence, except for the development of a small abscess in the abdominal wall. This subsided after incision and drainage. The enterostomy tube was removed on the sixteenth postoperative day and the patient was dismissed from the Clinic on Oct. 12, 1938, about a month after operation. At this time she was free from all pain and a recent communication revealed that she had had no recurrence of the symptoms which she had experienced prior to operation.

The pathologist who studied the specimen removed at operation reported that a chronic penetrating type of ulcer was situated at the junction of the distal portion of ileic mucosa with the Meckel's diverticulum, and that heterotopic gastric mucosa was present in the diverticulum (Fig. 1 a and b). The heterotopic gastric mucosa was of the fundic type and contained many parietal, acid secreting cells.

CASE 2—The patient was a man 48 years old who was first seen at the Clinic in 1924, at which time he had a rather characteristic history. Roentgenologic evidence of a duodenal ulcer with considerable deformity of the duodenum had been noted. Following medical treatment he had responded satisfactorily and had remained in good health until two months before the admission which primarily con-

cerns this report. The second admission of this patient to the clinic was on Sept. 29, 1936. For two months before his admission he had been experiencing lower abdominal colicky pains which seemed to have some tendency to be more severe in the right lower abdominal quadrant. Some degree of anorexia and much gaseous indigestion which was relieved by alkalis had been present. Twenty-four hours before admission the pains had been severe enough to necessitate the patient's sitting up in a chair all night, and he had obtained some relief after an enema.



Fig. 1.—*a* Mucosal ulcer at the junction of the distal portion of the ileac mucosa and eosin,  $\times 215$ . *b* Atrophic gastric mucosa,  $\times 150$ .

At the time of the patient's admission to the hospital there was clinical and physical evidence of subacute intestinal obstruction. Results of complete examination of the blood, including erythrocyte and leucocyte counts, and determinations of hemoglobin, urea, chlorides, and carbon dioxide combining power, all were negative. Results of roentgenologic examination of the thorax were negative. A plain roentgenogram of the abdomen revealed considerable dilatation of the left half of the transverse and descending portions of the colon, although a roentgenogram of the colon disclosed nothing abnormal. Roentgenologic examination made after the

patient had taken a barium meal showed the presence of an obstructing lesion within approximately 30 inches (76 cm.) of the ileocecal valve. It was visualized on the right side at about the level of the fourth lumbar vertebra. In view of these observations a diagnosis of subacute intestinal obstruction was made, with the possibility in mind that a malignant process might involve the lower portion of the ileum.

On Oct. 9, one week after admission, this patient underwent surgical exploration for the obstructing lesion in the lower part of the ileum. The operation was performed by Dr. J. deJ. Pemberton of the surgical staff. A lesion was found in the



FIG. 2.—*a* Section through ulcerating portion of lesion (hematoxylin and eosin,  $\times 110$ ). *b* Glandular tissue lining diverticulum. Note typical gastric type of glands with parietal cells (hematoxylin and eosin,  $\times 225$ ).

lower portion of the ileum which was producing rather marked obstruction. Huge dilatation of that part of the bowel proximal to the lesion was observed. It was not possible definitely to identify the character of the obstructive process, but it seemed to be a narrow tumor somewhat similar in shape to a napkin ring, involving the ileum with an extensive inflammatory reaction in the tissue around it. Lateral anastomosis was done; no attempt was made to remove the lesion. The patient made an uneventful convalescence, and on Nov. 3 a secondary operation was performed and further surgical exploration was carried out. Arising from the bowel at a point distal to the site of the previous anastomosis at right angles was a Meckel's diverticulum which was about  $1\frac{1}{2}$  inches (about 3.5 cm.) in diameter and 3 inches (about 8 cm.) long. The Meckel's diverticulum was adherent posteriorly to the bowel. It contained an ulcerating lesion and was producing obstruction. The diverticulum was removed, and the stump was turned in with three rows of chromic catgut sutures and one row of silk sutures. The patient made an uneventful recovery and has remained in excellent health to the time of this report.

Microscopic examination of tissue from the ulcerating lesion as shown in Fig. 2a and examination of the glandular elements contained in the mucosa which lined the diverticulum in the region of the ulcer showed typical gastric-type glands which contained many parietal cells (Fig. 2b). Rather marked associated diverticulitis and peridiverticulitis had been present.

#### COMMENT

In both of these cases it would appear, after careful gross and microscopic examination of the specimens removed at operation, that intrinsic intestinal obstruction had developed in the ileum as a result of the inflammatory reaction associated with active ulceration, similar to that of peptic ulcers, in or near a Meckel's diverticulum which was found to contain gastric mucosa with typical parietal cells. This type of obstruction, since it is of an intrinsic nature, is similar to that occurring in the duodenum secondary to peptic ulceration. This type of obstruction is distinct from that usually associated with a complicated Meckel's diverticulum, which is of an extrinsic or mechanical nature and which results from the formation of adhesions and inflammatory exudate about a Meckel's diverticulum which has perforated, with the subsequent occurrence of peritonitis.

Halstead in 1902 carefully analyzed and classified the types of intestinal obstruction which result from Meckel's diverticulum, but in the 69 cases of such obstruction he collected from the literature, he found none of an intrinsic nature. Not until some time after his report was it appreciated that frequently the ulcers occasionally present in Meckel's diverticula are similar to peptic ulcers. Although none of the cases which formed the basis of Halstead's report were similar to the 2 we have presented, he included in his classification a group which would include intrinsic intestinal obstruction caused by peptic ulcer in a Meckel's diverticulum, although he did not mention the complication of peptic ulcer. "Chronic inflammation of the diverticulum and of the adjacent portion of the intestine, with cicatricial narrowing of the gut just above the diverticulum, can be the cause of obstruction. This may happen in free and in attached diverticula. The diverticulum becomes

filled with fecal matter or concretions, and the resulting inflammation extends to the intestine, ulceration and cicatrization follow, and obstruction finally develops."

The fact that peptic ulceration in or near a Meckel's diverticulum may result in hemorrhage, penetration, or perforation with secondary extrinsic obstruction has been observed not infrequently in recent years. We believe that the 2 cases reported herein are the first reported in which proved peptic ulcer in Meckel's diverticulum resulted in intrinsic intestinal obstruction.

#### REFERENCES

1. Schaetz, G.: Quoted by Aschner, P. W., and Karelitz, Samuel: Peptic Ulcer of Meckel's Diverticulum and Ileum, *Ann. Surg.* 91: 573-582, 1930.
2. Carlson, L. A.: Quoted by Bussey.<sup>3</sup>
3. Bussey, C. D.: Histopathology of Meckel's Diverticulum, Thesis, University of Minnesota Graduate School, 1938.
4. Hudson, H. W., Jr., and Koplik, L. H.: Meckel's Diverticulum in Children: a Clinical and Pathologic Study; With a Report of Thirty-Two Cases, *New England J. Med.* 206: 827-840, 1932.
5. Halstead, A. E.: Intestinal Obstruction From Meckel's Diverticulum, *Ann. Surg.* 35: 471-494, 1902.
6. Deetz, E.: Quoted by Johnston, L. B., and Renner, George, Jr.: Peptic Ulcer of Meckel's Diverticulum; a Report of Two Cases and a Review of the Literature, *Surg., Gynec. & Obst.* 59: 198-209, 1934.
7. Cobb, D. B.: Meckel's Diverticulum With Peptic Ulcer, *Ann. Surg.* 103: 747-768, 1936.
8. Tillmanns, Lexer, Denucé, Rosthorn, Stone, and Taylor, A. L.: Quoted by Lindau and Wulff.<sup>9</sup>
9. Lindau, Arvid, and Wulff, Helge: The Peptic Genesis of Gastric and Duodenal Ulcer; Especially in the Light of Ulcers in Meckel's Diverticulum and the Postoperative Ulcers in the Jejunum, *Surg., Gynec. & Obst.* 53: 621-634, 1931.
10. Brown, P. W., and Pemberton, J. deJ.: Solitary Ulcer of the Ileum and Ulcer of Meckel's Diverticulum, *Ann. Int. Med.* 9: 1684-1702, 1936.



# CHYLOTHORAX AND CHYLOPERITONEUM

## EFFECTS OF REINTRODUCTION OF ASPIRATED CHYLE

JAMES MAXWELL LITTLE, PH.D., WINSTON-SALEM, N. C.,  
CARRINGTON HARRISON, M.D., NASHVILLE, TENN., AND  
ALFRED BLALOCK, M.D., BALTIMORE, MD.

*(From the Departments of Biochemistry and Surgery of Vanderbilt University,  
Nashville, Tenn.)*

APPROXIMATELY 50 cases of traumatic and 100 cases of non-traumatic chylothorax have been reported in the literature. No attempt will be made to review these reports. The nontraumatic ones were reviewed very adequately by Yater<sup>1</sup> in 1935. We are in the peculiar position in the present report in not knowing whether the chylothorax and chyloperitoneum were traumatic or nontraumatic in origin. The history of injury suggests trauma as the etiological agent, but the findings are indicative of a nontraumatic basis. The case is reported not because of the rarity of the condition but because of the bizarre associated findings, because the effects of reintroducing intravenously some of the aspirated chyle were determined, and because many chemical studies of interest were carried out. No previous patient has been given such large quantities of chyle. Bauersfeld<sup>2</sup> reported the effects of the intravenous injection of 1,200 c.c. of chyle.

### CLINICAL COURSE OF PATIENT

E. G., a married white female, 17 years of age, was admitted to the Vanderbilt Hospital on Dec. 3, 1939. The patient stated that she was in good health until two and one-half months prior to admission when in an automobile accident she was thrown clear of the car. She was able to walk after the accident, but a few minutes subsequently pain was experienced in the left shoulder and left supraclavicular region. Respiratory and shoulder movements were without influence on the pain. This pain subsided after about four days. It should be stated at this time that the husband of the patient was of the opinion that there had been a moderate increase in the size of her abdomen prior to the accident.

Two weeks following her injury, the patient had an attack of tonsillitis which subsided in a few days. There were no further complaints for the next two weeks, at the end of which time a tender swelling about the size of a hen's egg appeared in the left supraclavicular region. This swelling persisted for a week. Five weeks prior to admission, she noticed that she was breathing faster and that deep inspiration was more difficult. A moderate amount of pain in the chest and left supraclavicular region was experienced. Three weeks before admission, or seven weeks following the accident, it was noted that the abdomen was increasing in size and the patient complained of a feeling of fullness and of dyspnea. Her family physician was consulted and 1,500 c.c. of milky fluid were removed from the left pleural cavity. Thoracentesis was repeated on three other occasions prior to admission, and each aspiration resulted in a diminution in her dyspnea and discomfort.

Examination on Dec. 3, 1939, showed the patient to be well developed and fairly well nourished, although there was slight wasting of the extremities. The weight of the patient was 150 pounds and she stated that this was 10 pounds greater than her average. There were no scars or abnormal masses in the neck. Respiratory excursions of the left chest were diminished and the findings on palpation and percussion indicated the presence of a great deal of fluid in the left pleural cavity. No abnormalities of the right side of the chest were noted. There was marked abdominal distention and signs indicative of much free fluid were elicited. There were no palpable abdominal masses, no tenderness, and no muscular rigidity. Pelvic and rectal examinations were negative. In the lower dorsal, sacral, and lumbar regions, there was moderate pitting edema which was probably due to the extravasation of chyle at the site of one of the pleural taps. The temperature was normal, the white blood cell count was 5,800, and the urine and stools showed no abnormality. The specific gravity of the urine was 1.026. The supravital differential count of the blood revealed 70.5 per cent polymorphonuclears, 16.5 per cent lymphocytes, and 13 per cent monocytes. The venous pressure was 225 mm. water by the Lyons-Kennedy-Burwell's technique. This is a moderate but not necessarily a significant elevation. Fluoroscopic and x-ray examinations of the heart, lungs, ribs, spine, clavicles, and the gastrointestinal tract showed no abnormalities except for the presence of fluid in the peritoneal and left pleural cavities.

Milky fluid was aspirated from both the left pleural cavity and the peritoneal cavity, and analyses, which will be considered subsequently, showed it to be chyle. Therapy consisted in the main of placing the patient on a fat-free diet, of aspirating frequently part of the chyle from the pleural and peritoneal cavities, and of introducing intravenously part of that which was obtained from the pleural cavity. This latter procedure was performed by the use of a closed system, consisting of two needles, rubber tubing, a three-way stopcock and a syringe, the chyle being aspirated from the chest and then immediately injected intravenously. Usually the patient had chilly sensations with vague feelings of discomfort following the introduction of chyle, but there were no severe reactions.

From Dec. 3 to Feb. 8, approximately nine weeks, the patient was on a fat-free diet which, by calculation, contained less than 5 Gm. of fat per day. During the succeeding week, she was on a low-fat diet which contained approximately 40 Gm. of fat per day. During this period of ten weeks, 29,730 c.c. of chyle were removed from the peritoneal cavity, 16,060 c.c. of chyle removed from the left pleural cavity and 11,385 c.c. removed from the chest were injected intravenously. While the patient was on a fat-free or a low-fat diet, there was a marked decrease in the total lipid concentration of the chylous fluid. The diet, however, did not cause a cessation of the accumulation of fluid, and after Feb. 13, the patient received the usual hospital diet calculated to yield 3,000 calories. This alteration in the diet resulted in a sharp and marked increase in the total lipid concentration of the fluid.

It was decided that an exploration of the thoracic duct was indicated and this was performed on Feb. 28, 1940. An incision was made in the left supraclavicular region. In the region of the junction of the internal jugular and subclavian veins, there were several large lymph vessels which contained chyle and the lymph nodes were large, soft, and white in color. No injury to the lymph channels was demonstrated. Several of the lymph channels were partially thrombosed. The internal jugular vein was a thick cord, the lumen being entirely occluded by a thrombus. The subclavian vein was not opened, but its walls appeared to be thickened. Before having determined that venous thrombosis was present, several of the dilated lymph ducts were ligated. The incision was closed without drainage.

Four days following the operation, the patient complained of numbness and tingling of both feet and lower legs. The feet felt cold and appeared pale. Pulsations could not be felt over the femoral, popliteal, posterior tibial, and dorsalis pedis arteries of both lower extremities. The condition of the legs and feet varied from time to time. Pulsations were present at times and absent at others. She

# CHYLOTHORAX AND CHYLOPERITONEUM

## EFFECTS OF REINTRODUCTION OR ASPIRATION CHYLE

JAMES MAXWELL LITTLE, PH.D., WINSTON-SALEM, N. C.,

CARRINGTON HARRISON, M.D., NASHVILLE, TENN., AND

ALFRED BLALOCK, M.D., BALTIMORE, MD.

*(From the Departments of Biochemistry and Surgery of Vanderbilt University, Nashville, Tenn.)*

APPROXIMATELY 50 cases of traumatic and 100 cases of non-traumatic chylothorax have been reported in the literature. No attempt will be made to review these reports. The nontraumatic ones were reviewed very adequately by Vater<sup>1</sup> in 1935. We are in the peculiar position in the present report in not knowing whether the chylothorax and chyloperitoneum were traumatic or nontraumatic in origin. The history of injury suggests trauma as the etiological agent, but the findings are indicative of a nontraumatic basis. The case is reported not because of the rarity of the condition but because of the bizarre associated findings, because the effects of reintroducing intravenously some of the aspirated chyle were determined, and because many chemical studies of interest were carried out. No previous patient has been given such large quantities of chyle. Bauersfeld<sup>2</sup> reported the effects of the intravenous injection of 1,200 c.c. of chyle.

### CLINICAL COURSE OF PATIENT

J. G., a married white female, 17 years of age, was admitted to the Vanderbilt Hospital on Dec. 3, 1939. The patient stated that she was in good health until two and one half months prior to admission when in an automobile accident she was thrown clear of the car. She was able to walk after the accident, but a few minutes subsequently pain was experienced in the left shoulder and left supraclavicular region. Respiratory and shoulder movements were without influence on the pain. This pain subsided after about four days. It should be stated at this time that the husband of the patient was of the opinion that there had been a moderate increase in the size of her abdomen prior to the accident.

Two weeks following her injury, the patient had an attack of tonsillitis which subsided in a few days. There were no further complaints for the next two weeks, at the end of which time a tender swelling about the size of a hen's egg appeared in the left supraclavicular region. This swelling persisted for a week. Five weeks prior to admission, she noticed that she was breathing faster and that deep inspiration was more difficult. A moderate amount of pain in the chest and left supraclavicular region was experienced. Three weeks before admission, or seven weeks following the accident, it was noted that the abdomen was increasing in size and the patient complained of a feeling of fullness and of dyspnea. Her family physician was consulted and 1,500 cc of milky fluid were removed from the left pleural cavity. Thoracentesis was repeated on three other occasions prior to admission, and each aspiration resulted in a diminution in her dyspnea and discomfort.

TABLE I  
RECORD OF THORACENTESIS, PARACENTESIS, AND INTRAVENOUS CHYLE INJECTION

DATE	THORACENTESIS (C.C.)	PARACENTESIS (C.C.)	CHYLE TRANSFUSION	DATE	THORACENTESIS (C.C.)	PARACENTESIS (C.C.)	CHYLE TRANSFUSION
12/ 4/39	500			3/4	1,600	4,300	
12/ 5/39		80		3/5	2,700		
12/ 7/39	600		500	3/12	1,000		1,000
12/ 9/39	600		600	3/18	1,000		1,000
12/11/39	500		500	3/19		8,500	
12/14/39		1,500		3/20	1,000		1,000
12/19/39	1,000		1,000	3/25	1,000		1,000
12/21/39		3,200		3/28		8,100	
12/28/39	800		800	4/ 1	1,000		1,000
12/29/39		7,000		4/ 3	2,000		1,000
12/30/39	900		900	4/ 5	1,000		1,000
1/ 2/40	550		550	4/ 7		9,500	
1/ 4/40	800		525	4/ 9	100		100
1/ 9/40	950		950	4/12	1,000		1,000
1/10/40		3,500		4/13	1,000		1,000
1/12/40	500		500	4/14		7,000	
1/16/40	590		590	4/19		6,000	
1/19/40	700		700	4/26		6,700	
1/20/40		3,500		5/ 3	1,000		
1/21/40	330		330	5/ 6		6,000	
1/23/40	960		960	5/12		6,000	
1/24/40		3,350		5/16	1,250		
1/25/40	1,750			5/19		5,000	
1/30/40	430		430	5/24	2,100		
2/ 1/40	1,900	3,500		5/27		7,000	
2/ 6/40		3,500		6/ 2		6,000	
2/ 7/40	700			6/ 4	1,700		
2/15/40	1,000		1,000	6/ 7		8,000	
2/16/40		5,000		6/14		7,000	
2/19/40	1,000		1,000	6/15	2,100		
2/24/40	500						
2/25/40		8,400					
2/26/40	1,000		1,000		42,110	138,230	22,485

TABLE II  
CONCENTRATION OF LIPIDS IN FLUID FROM THORAX (MG. %)

DATE	FREE CHO-LESTEROL	ESTERIFIED CHO-LESTEROL	RATIO OF ESTERIFIED TO FREE CHO-LESTEROL	LIPID PHOS-PHORUS	PHOS-PHATIDE	TOTAL LIPID CARBON	NEUTRAL FAT	TOTAL LIPIDS
12/ 4/39	22	41	1.85	3.1	73	1,975	1,268	1,422
12/ 9/39	26	43	1.65	1.2	51	720	798	948
12/28/39	21	40	2.00	3.0	70	466	457	616
1/19/40	19	60	3.16	3.4	80	463	330	530
1/25/40	18	42	2.33	3.4	81	377	330	500
1/30/40	22	28	1.27	3.9	92	531	345	706
2/ 1/40	18	43	2.39	2.7	64	515	523	678
2/15/40	18	29	1.61	3.9	92	842	958	1,117
2/26/40	27	35	1.30	8.0	189	1,980	2,353	2,628
3/ 5/40	23	39	1.70	5.4	128	1,579	1,876	2,003
3/12/40	28	46	1.64	12.2	310	3,177	3,810	4,226
3/18/40	36	41	1.14	13.0	309	3,168	3,721	4,122
4/ 1/40	16	51	3.19	9.8	231	2,572	2,768	3,101

\*Drawn day after 500 cc. of chyle were given to patient.

complained of intense pain most of the time. There was a slow improvement, but evidences of impairment of circulation of the extremities persisted. It was our impression that the disturbance consisted of arterial spasm secondary to thrombophlebitis. On several occasions there was a less evident abnormality of the circulation of the arms. In addition, there was what appeared to be a thrombosed vein at the umbilicus.

The quantities of chyle that were aspirated and reintroduced up to Feb. 15, the time at which the fat free diet was terminated, have been enumerated. From Feb. 15 until her discharge from the hospital on June 15, a period of four months, 198,500 c.c. of chyle were removed from the abdominal cavity, 26,050 c.c. from the left pleural cavity, and of this latter amount, 11,100 c.c. were given intravenously. From March 10 to 17, heparin was administered intravenously by the continuous method, the clotting time being maintained at approximately twenty minutes. The clotting time on a previous examination was 3.5 minutes. The heparin was given with the hope that canalization of thrombosed veins would occur. No evidence of improvement resulted. No chyle was injected intravenously after April 13. Reasons for stopping the injection of chyle were that there was no apparent clinical improvement and that it became almost impossible to find a patent vein. Furthermore, the question arose as to whether or not the direct introduction of chyle into the blood stream might not be causing additional thrombosis.

As has been stated, the patient was discharged from the hospital on June 15, 1940. Her condition was less satisfactory than at the time of her admission more than six months previously. The extremities and face had become markedly emaciated. Chyle continued to accumulate, at least in the peritoneal cavity, as rapidly as at the onset. There was still evidence of disturbance of circulation of the legs and she frequently complained of pain.

It has now been almost a year since the patient returned to her home. Her condition has not changed markedly during this time. She is able to be up for short periods but tires very easily. Fluid has continued to accumulate in the peritoneal cavity from which it is removed once or twice weekly. The average quantity removed per day has been 1 liter. During the approximately eighteen months that the patient has been ill, more than 500 liters of chyle have been removed from the pleural and peritoneal cavities.

#### CHEMICAL STUDIES

In view of the probable disturbances in lipid metabolism and plasma protein concentrations entailed by the loss of chyle rich in lipid and containing a moderate quantity of protein, a rather extensive chemical investigation of the chyle and plasma was undertaken.

In obtaining the data reported here, all lipid determinations were made using the procedure of Kirk, Page and Van Slyke<sup>4</sup> with the following modifications: (a) extraction of lipids at room temperature as given by Boyd;<sup>5</sup> (b) substitution of 0.18 c.c. of saturated aqueous solution of sodium hydroxide plus 2 c.c. of ethyl alcohol for the procedure given by Kirk and co-workers for the saponification of total cholesterol; and (c) substitution of the procedure of Man<sup>6</sup> for the evaporation of the alcohol-ether extract prior to extraction with petroleum ether. The observed free cholesterol values are too high and may be corrected<sup>7</sup> by multiplying by 0.8. The total proteins and albumin were determined by a modification of Howe's method.<sup>8</sup> The determinations of colloidal osmotic pressure were made using the method of Wells.<sup>9</sup>

TABLE IV  
CONCENTRATION OF LIPIDS IN PLASMA (MG. %)

DATE	FREE CHOLESTEROL	ESTERIFIED CHOLESTEROL	RATIO OF ESTERIFIED TO FREE CHOLESTEROL	LIPID PHOSPHORUS	PHOSPHATIDE	TOTAL LIPID CARBON	NEUTRAL FAT	TOTAL LIPIDS
12/ 9/39	48	121	2.52	5.1	120	419	173	545
12/28/39	44	137	3.11	6.2	144	426	135	555
1/ 8/40	46	129	2.81	4.2	98	399	152	514
1/19/40	42	101	2.41	6.3	148	389	153	514
1/30/40	44	113	2.57	7.9	185	435	156	576
2/14/40	42	108	2.57	2.6	61	359	176	462
2/21/40	53	113	2.13	6.0	140	450	206	590
3/19/40	48	127	2.65	3.1	72	389	163	498
4/ 1/40*	54	169	3.13	3.3	77	470	181	598
4/ 1/40†	46	128	2.78	9.6	226	1,328	1,268	1,756
4/ 1/40‡	54	118	2.19	6.5	152	447	181	587

\*Drawn just before injection of chyle.

†Drawn immediately after injection of 1,000 c.c. of chyle.

‡Drawn 5½ hours after injection of chyle.

The data obtained for total protein, albumin, and osmotic pressure will be found in Tables V, VI, and VII. There is no significant difference in the protein concentration of fluid from the thorax and that from the peritoneum. The average concentration in the former was 3.16 per cent and in the latter 3.08 per cent. The albumin-globulin ratios were quite variable, but with one exception they are always above 1.5. None of the variations in diet had an effect upon the concentration of protein in the fluids. The results obtained for serum proteins are of interest, in that in spite of a moderately high protein diet (75 to 80 gm. per day) and continual injection of chyle the serum proteins and serum colloidal osmotic pressure progressively decreased. Both were certainly approaching a critical level. This decrease must be attributed to the enormous loss of protein in the chyle which was removed but not returned to the circulation.

TABLE V  
PROTEIN DATA ON FLUID FROM THORAX

DATE	TOTAL PROTEIN %	ALBUMIN %	GLOBULIN %	A/G RATIO	OSMOTIC PRESSURE DETERMINED MM. H <sub>2</sub> O
12/ 4/39	3.38	2.11	1.27	1.66	112 150
12/ 9/39	3.48	2.08	1.40	1.49	
12/28/39	3.22	2.31	0.91	2.54	
1/19/40	3.11	1.90	1.21	1.57	
1/25/40	2.78	2.17	0.61	3.56	
2/ 1/40	3.10	2.04	1.06	1.92	
2/15/40	3.02	1.91	1.11	1.72	
2/26/40	2.72	1.86	0.86	2.16	
3/ 5/40	4.55	2.63	1.92	1.37	
3/25/40	3.40	1.55	1.85	0.84	
4/ 1/40	2.05	1.87	0.18	10.39	

From Table I it will be seen that over a period of approximately six months 180,300 c.c. of chylous fluid were removed from the thorax and peritoneum, while 22,500 c.c. were returned by intravenous injection. The lipid distribution in samples of these fluids drawn at various times is found in Tables II and III. As stated previously, from Dec. 3 until

TABLE III  
CONCENTRATION OF LIPIDS IN FLUID FROM PERITONEUM (MG. %)

DATE	FREE CHO- LESTEROL	ESTER- IFIED CHOLES- TEROL	RATIO OF ESTER- IFIED TO FREE CHOLES- TEROL	LIPID PHOS- PHORUS	PHOS- PHAT- IDE	TOTAL LIPID CARBON	NEUTRAL FAT	TOTAL LIP- IDS
12/ 5/39	23	43	1.87	2.7	63	828	926	1,085
12/15/39	21	43	2.05	1.1	25	378	375	494
12/24/39	22	40	1.82	2.2	52	346	314	456
1/24/40	31	50	1.17	1.0	91	619	605	818
2/ 1/40	23	48	2.09	2.2	51	489	487	612
2/ 6/40	20	36	1.80	3.1	73	588	621	778
2/16/40*	27	47	1.74	5.2	122	1,116	1,250	1,478
5/ 6/40	20	49	2.45	6.5	153	2,310	2,803	3,059

\*Drawn day after 500 c.c. of cream were given to patient.

Feb. 8, the patient was on a fat-free diet, which, by calculation, contained less than 5 Gm. of fat per day; and from Feb. 8 to 15 she was on a low-fat diet which contained approximately 40 Gm. of fat per day. After Feb. 15 the patient received the usual hospital diet calculated to yield 3,000 calories. While the patient was on a fat-free and low-fat diet there was a marked decrease in the total lipid concentration of the chylous fluids. This decrease was due largely to the neutral fat fraction, since there was no consistent decrease in the other lipid fractions. When the patient was removed from the low-fat diet there was a sharp and marked increase in the total lipid concentration of the chylous fluid, which is due not only to the neutral fat but also to the phosphatide fraction.

From the data given in Table IV it will be seen that the concentration of the various plasma lipid fractions remained remarkably constant throughout the period of observation. Whether this is due to a complete lack of effect of dietary regime, or whether it is due to the continual augmentation of plasma lipids by means of injections of chyle cannot be determined. It is of great interest that throughout the period of observation, the lipid concentrations are either only slightly below or within the normal range found by Page and his associates<sup>10</sup> for normal men. Another point of interest is the rapid removal of lipids from the blood after injection of chyle. Five and one-half hours after injection of chyle the concentration of the lipid fractions had returned to the preinjection level, with the exception of phosphatides which were still elevated.

weeks. In analyzing the histories of thirty-three patients with traumatic chylothorax, Shackelford and Fisher<sup>11</sup> found that this interval is most commonly four days but that it varied from two days to six weeks. The collection of chyle in both the pleural and peritoneal cavities is somewhat against trauma as the etiological agent. The absence of a penetrating wound does not exclude trauma as the cause. Most instances of traumatic chylothorax have followed crushing injuries, falls from a height, and blows on the chest.

The most common cause of nontraumatic chylothorax is malignancy. Despite a careful search, no evidence of malignancy was found in our patient. The fact that she is alive more than eighteen months following the onset of this disorder is evidence against a metastatic tumor as a cause of the blockage. Other causes of nontraumatic chylothorax include tuberculosis and venous thrombosis. Yater<sup>1</sup> has considered these and other etiological agents in detail. The findings at operation, i.e., thrombosis of the internal jugular vein, and the subsequent disturbances of the circulation of the extremities which were probably due to thrombophlebitis, lead us to believe that the most likely cause for the chylothorax and chyloperitoneum in our patient was multiple venous thrombosis. It is possible that the thrombosis of the internal jugular vein was secondary to traumatic rupture of the thoracic duct, but it appears more likely that the thrombosis was primary rather than secondary. This explanation is more compatible with the finding of evidence of thrombosis elsewhere in the body.

It is well known, furthermore, that the lymphatic system as well as the blood vascular system is abundantly supplied with collateral channels. The thoracic duct of man may be ligated and other lymph vessels will enlarge sufficiently to conduct the lymph to the venous system. It is usually impossible in dogs to cause total lymph blockage by the use of multiple stage operations in which many lymph vessels are ligated or destroyed. On the other hand, Blalock, Cunningham, and Robinson<sup>12</sup> found that chylothorax developed in approximately one-half of the dogs and cats in which the superior vena cava was occluded by a ligature. If the death of these animals was prevented by the aspiration of the chyle, usually other lymph vessels would enlarge with the passage of time and the chyle would be returned to the venous system.

It is possible that the lymph of this patient possessed some property which caused an injury to veins at the points of junction of the lymphatic and venous systems. Furthermore, it is quite possible that the reinjection of chyle resulted in a greater degree of venous thrombosis than would have occurred otherwise. Although the observation may not be pertinent to this discussion, Johnson and Freeman<sup>13, 14</sup> noted the existence in dogs of a hemolytic agent in lacteal lymph and to a lesser extent in thoracic duct lymph during the absorption of ingested fat. We found no evidence of hemolysis after the injection of chyle into the



It has been assumed, in some reports, that a limitation of the fluid intake and dietary fat would reduce the formation of chyle, but there has been no quantitative evidence to support this assumption. The patient reported here was maintained on a fat-free diet for sixty-five days during which time a total of 44,790 c.c. of fluid were withdrawn for an average of 689 c.c. per day. For a period of sixty-three days, when the patient received the regular hospital diet, a total of 75,700 c.c. of fluid were withdrawn for an average of 1,202 c.c. per day. This apparently supports the assumption, and there is no doubt but that the chyle formation is affected by a low-fat intake. However, in interpret-

TABLE VI  
PROTEIN DATA ON FLUID FROM PERITONEUM

DATE	TOTAL PROTEIN %	ALBUMIN %	GLOBULIN %	A/G RATIO	OSMOTIC PRESSURE DETERMINED MM. H <sub>2</sub> O
12/ 5/39	3.79	2.51	1.25	2.02	134 119
12/21/39	3.53	2.98	0.55	5.42	
2/ 1/40	2.79	1.91	0.88	2.17	
2/16/40	2.89	2.18	0.71	3.07	
5/ 6/40	2.39	1.64	0.75	2.19	

TABLE VII  
PROTEIN DATA ON SERUM

DATE	TOTAL PROTEIN %	ALBUMIN %	GLOBULIN %	A/G RATIO	OSMOTIC PRESSURE DETERMINED MM. H <sub>2</sub> O
12/ 9/39	6.36	4.06	2.30	1.77	278 268 230 220 218 228 220
12/28/39	6.65	4.05	2.60	1.56	
1/19/40	5.57	3.09	2.48	1.25	
1/30/40	6.10	---	---	---	
2/ 1/40	5.04	2.98	2.06	1.45	
2/14/40	5.90	3.79	2.11	1.80	
2/16/40	5.03	3.11	1.92	1.62	
3/18/40	4.51	---	---	---	
3/19/40	4.05	---	---	---	
4/ 1/40	4.70	3.93	0.77	5.10	

ing these results another factor must be considered. During most of the time when the usual diet was being given the serum colloidal osmotic pressure was much lower than during the period of a fat-free diet. On three occasions the venous pressure was found to be 250, 262, and 230 mm. of water. Thus there was little margin between the venous pressure and colloidal osmotic pressure, so that the net filtration from the capillaries was probably greatly increased, thereby increasing the volume of lymph.

#### DISCUSSION

The interval between the injury to the patient and the evidence of the accumulation of chyle in the pleural and peritoneal cavities was five

weeks. In analyzing the histories of thirty-three patients with traumatic chylothorax, Shackelford and Fisher<sup>11</sup> found that this interval is most commonly four days but that it varied from two days to six weeks. The collection of chyle in both the pleural and peritoneal cavities is somewhat against trauma as the etiological agent. The absence of a penetrating wound does not exclude trauma as the cause. Most instances of traumatic chylothorax have followed crushing injuries, falls from a height, and blows on the chest.

The most common cause of nontraumatic chylothorax is malignancy. Despite a careful search, no evidence of malignancy was found in our patient. The fact that she is alive more than eighteen months following the onset of this disorder is evidence against a metastatic tumor as a cause of the blockage. Other causes of nontraumatic chylothorax include tuberculosis and venous thrombosis. Yater<sup>1</sup> has considered these and other etiological agents in detail. The findings at operation, i.e., thrombosis of the internal jugular vein, and the subsequent disturbances of the circulation of the extremities which were probably due to thrombophlebitis, lead us to believe that the most likely cause for the chylothorax and chyloperitoneum in our patient was multiple venous thrombosis. It is possible that the thrombosis of the internal jugular vein was secondary to traumatic rupture of the thoracic duct, but it appears more likely that the thrombosis was primary rather than secondary. This explanation is more compatible with the finding of evidence of thrombosis elsewhere in the body.

It is well known, furthermore, that the lymphatic system as well as the blood vascular system is abundantly supplied with collateral channels. The thoracic duct of man may be ligated and other lymph vessels will enlarge sufficiently to conduct the lymph to the venous system. It is usually impossible in dogs to cause total lymph blockage by the use of multiple stage operations in which many lymph vessels are ligated or destroyed. On the other hand, Blalock, Cunningham, and Robinson<sup>12</sup> found that chylothorax developed in approximately one-half of the dogs and cats in which the superior vena cava was occluded by a ligature. If the death of these animals was prevented by the aspiration of the chyle, usually other lymph vessels would enlarge with the passage of time and the chyle would be returned to the venous system.

It is possible that the lymph of this patient possessed some property which caused an injury to veins at the points of junction of the lymphatic and venous systems. Furthermore, it is quite possible that the reinjection of chyle resulted in a greater degree of venous thrombosis than would have occurred otherwise. Although the observation may not be pertinent to this discussion, Johnson and Freeman<sup>13, 14</sup> noted the existence in dogs of a hemolytic agent in lacteal lymph and to a lesser extent in thoracic duct lymph during the absorption of ingested fat. We found no evidence of hemolysis after the injection of chyle into the

vascular system of this patient. Since we had some doubts as to the advisability of injecting intravenously large quantities of chyle, Dr. Emmett Holt<sup>17</sup> was consulted, and it was his opinion that the introduction of the patient's own chyle would not be more dangerous than the use of emulsified fat provided the particle size was 1 micron or less with only an occasional particle as large as 3 microns.

One may find in the literature many analyses of chylous effusions in which methods with varying degrees of refinement were used. The reports of Harrel, Street, and Reiser<sup>18</sup> and Robinson and co-workers<sup>17</sup> are the most complete as far as lipid fractions are concerned. Harrel and his co-workers give a complete lipid analysis of fluids obtained from the right and left pleural cavities and peritoneal cavity. Robinson and co-workers determined the lipid fractions of fluids obtained from animals in which the superior vena cava had been ligated. Cookson and Slade<sup>19</sup> report very complete analytical data on a sample of chyle obtained from a patient.

We have found only one report in which the effect of treatment on the composition of a chylous effusion was studied. Schaefer<sup>19</sup> studied the effect of a fat-free diet in which the proportion of carbohydrate and protein was varied. The fat content of the chyle progressively decreased but variations of the dietary protein or carbohydrate produced no consistent effects.

In no previous instances have the effects of treatment (low-fat diet and injection of chyle) upon the chyle and serum proteins and upon the plasma lipids been determined. The plasma lipids were maintained at a normal or slightly less than normal level. We were unsuccessful, however, in preventing a rather critical decrease in the serum protein concentration and serum colloidal osmotic pressure by the treatment that was used. Over a period of six months there was a net loss of chyle of 158,000 c.c. with an average protein content of 3 per cent, or a net loss of 4,740 Gm. of protein, which is approximately 25 Gm. per day. A large percentage of this was albumin. Madden and Whipple<sup>20</sup> have recently reviewed the source, production, and utilization of plasma proteins. They state that normal dogs have sufficient protein reserves to form a quantity of plasma protein one to two times the amount normally present in the circulation. Once this reserve is depleted the subsequent formation of plasma proteins is almost entirely dependent upon the quantity and quality of the dietary protein. Unfortunately records of food consumption were not kept in the case reported here, but it is very probable that the protein consumption was less than 80 Gm. daily. The declining serum protein concentration indicates that the protein consumption was insufficient to maintain the plasma protein level by regeneration. It would have been interesting to try the effect on regeneration of a diet containing gelatin, cystine, and tyrosine, which was found by Whipple and his co-workers to be very efficient in

animal experiments. The protein loss is very significant from the nutritional viewpoint and also in consideration of lymph production and it is our belief that it is more important in the bodily economy of the patient than the lipid loss. When it is realized that during her nineteen months of illness approximately 550 liters of chyle have been removed from the patient, representing a loss of approximately 16,000 Gm. of protein, it is surprising that her downhill course has not been even more rapid.

In reviewing our experience with this patient, it is evident that at least the following factors are in need of further study: (a) the effect of the dietary protein upon the regeneration of plasma proteins in patients subjected to a continuous loss of protein, as in the case here reported; (b) the possible efficacy of frequent plasma transfusions as a means of treatment; and (c) the effect of repeated injections of chyle upon the clotting time of the blood and upon the endothelium of the vascular system.

In summary, the clinical course of a patient with chylothorax and chyloperitoneum has been described. The effects of a fat-free diet and of reinjection of the aspirated chyle have been noted and the significance of the alterations has been discussed.

#### REFERENCES

1. Yater, W. M.: *Ann. Int. Med.* 9: 600, 1935.
2. Bauersfeld, E. H.: *J. A. M. A.* 109: 16, 1937.
3. Lyons, R. H., Kennedy, J. A., and Burwell, C. S.: *Am. Heart J.* 16: 675, 1938.
4. Kirk, E., Page, I. H., and Van Slyke, D. D.: *J. Biol. Chem.* 106: 203, 1934.
5. Boyd, E. M.: *J. Biol. Chem.* 114: 223, 1936.
6. Man, Evelyn B.: *J. Biol. Chem.* 117: 183, 1937.
7. Van Slyke, D. D.: Personal communication, 1940. Foleh, J., Schneider, H. A., and Van Slyke, D. D.: *J. Biol. Chem.* 133: 33, 1940.
8. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, 1932, Williams and Wilkins Co., vol. II, p. 691.
9. Wells, H. S.: *J. Tennessee Acad. Sc.* 8: 102, 1933.
10. Page, I. H., Kirk, E., Lewis, W. H., Jr., Thompson, W. R., and Van Slyke, D. D.: *J. Biol. Chem.* 111: 613, 1935.
11. Shackelford, R. T., and Fisher, A. M.: *South. M. J.* 31: 766, 1938.
12. Blalock, Alfred, Cunningham, R. S., and Robinson, C. S.: *Ann. Surg.* 104: 359, 1936.
13. Johnson, V., and Freeman, L. W.: *Am. J. Physiol.* 124: 466, 1938.
14. Freeman, L. W., and Johnson, V.: *Am. J. Physiol.* 130: 723, 1940.
15. Holt, L. Emmett, Jr.: Personal communication, 1940.
16. Harrell, G. T., Street, D. M., and Reiser, R.: *J. Lab. & Clin. Med.* 24: 1045, 1940.
17. Robinson, C. S., Cunningham, R. S., Blalock, A., Gray, Mary E., and Rogers, B. C.: *Arch. Path.* 24: 703, 1937.
18. Cookson, H. A., and Slade, D. A.: *Lancet* 2: 477, 1940.
19. Schaefer, R.: *Deutsches Arch. f. klin. Med.* 157: 69, 1927.
20. Madden, S. C., and Whipple, G. H.: *Physiol. Rev.* 20: 194, 1940.

# THE SURGICAL MANAGEMENT OF VARICOSE VEINS: IMPORTANCE OF INDIVIDUALIZATION IN THE CHOICE OF PROCEDURE\*

HENRY N. HARKINS, M.D., Ph.D., and RICHARD SCHUG, M.D.,  
DETROIT, MICH.

(From the Division of General Surgery, Department of Surgery,  
Henry Ford Hospital)

**V**ARICOSE veins have long been classified as a so-called minor surgical condition and in consequence their care in many cases has been relegated to residents and other younger surgeons. In only rare instances has a more experienced surgeon devoted enough time to the study of this subject to become well acquainted with the variations these cases may present. As a result, either a stereotyped operation is performed or the patient is treated by a physician who, not being a surgeon, has no choice but to use some medical treatment such as the injection of sclerosing solutions. While these latter treatments may have their place, only too often when a doctor has only one means of treatment at his disposal, he will use only that method.

The interest of one of us (H. N. H.) was aroused in this subject from being personally afflicted with the condition and from having had personal experience with sodium morrhuate injections, and later, more successfully, with surgical operative treatment. The present series represents the operations performed by the senior author (H. N. H.) during the year 1940 (Jan. 13, 1940, to Jan. 12, 1941). Operations on three of the sixty-three patients were done by two of the senior author's assistants under his direct supervision and using his methods. During this period a substantial number of other operations performed by other surgeons in the Henry Ford Hospital is not included in this series. The cases have not been followed long enough to observe the ultimate results. The present series does not, therefore, at all pretend to be a follow-up report, but merely is a presentation of the methods used by one of us over a one-year period.

## DIAGNOSTIC MEASURES

The following tests were used in diagnosis and determination of the type of therapy to be used:

1. *Inspection and Palpation.*—In general, cases with visible or palpable veins above the knee were considered as unsuitable for injection alone. The presence of edema was considered a contraindication to all modes of therapy (injection or ligation) until the edema was controlled.

\*Enlarged and brought up to date from a paper presented before the first annual meeting of the Central Surgical Association, Ann Arbor, Mich., March 1, 1941. An abstract of this paper was published in the Proceedings of the Association, Ann. Surg. 113: 1109-1111, 1941.

Received for publication, March 2, 1941.

Very superficial veins are stripped with difficulty as they are friable and attached to the dermis so that if they are to be removed, excision is preferable to stripping.

2. *Schwartz Test*.—Percussion with palpation of the impulse down the vein is often considered to be a sign of incompetent valves, but may occur in normal veins. This method, however, helps in tracing the course of veins, especially in obese patients.

3. *Perthes Test*.—

a. WITH TOURNIQUET.—With a high tourniquet, if the veins become more prominent on walking, a deep thrombosis is suspected. However, if there is a localized thrombosis below the tourniquet, the test would not necessarily rule it out. Similarly, however, if the test is normal, even if there is a localized deep thrombosis, unless by chance the detouring superficial veins just adjacent to it are operated upon, no harm will probably result. As a diagnosis before injection therapy, the theoretical objection is more valid.

b. WITH TIGHT RUBBER BANDAGE FROM ANKLE TO THIGH.—This will detect even a localized deep obstruction (tight bandage test of McCallig and Heyerdale, 1940).

4. *Trendelenburg Test*.—To avoid confusion as to "positive" and "negative" we use the terms normal, abnormal, and doubly abnormal. Normal means no filling from above after tourniquet release, abnormal means filling only from above indicating fossa ovalis leakage, while doubly abnormal means filling from both above and below indicating fossa ovalis leakage plus lower incompetent perforators.

5. *Mahorner-Ochsner Test (1938)*.—With a tourniquet high in the thigh complete emptying of the varicose veins on walking indicates incompetency only at the fossa ovalis. A control should always be done with the patient walking without a tourniquet as we have seen at least three patients where if this had not been done, the results would have been misleading. If the high tourniquet does not produce complete "walking-emptying," it is placed progressively lower until such an effect is obtained. This marks the site of the lowest incompetent perforator. The two-tourniquet test of Pratt (1939) appears to be of value, but we did not use it in the present series of cases.

6. *Harkins Test*.—This test, which we have also called the local Mahorner-Ochsner test, gives a horizontal as well as a vertical localization. For example, in a case where the Mahorner-Ochsner test shows the lowest perforator to be just above the knee, but yet the exact place on the circumference of the leg where this perforator is to be found is unknown, the following test is performed. The examiner sits on a very low stool at the side of the patient and places the middle finger of both hands on the most suspicious vein at this level. This is usually away from him over the medial condyle. His hands loosely surround the leg and the two thumbs are then placed for counter pressure on a relatively

vein-free area over the lateral condyle of the femur. The patient is instructed to keep the opposite foot motionless but to step alternately forward and backward five times with the other foot, the leg of which is being held all the time. An observation is then made, and in cases where the vein pressed upon is the chief culprit, as good emptying of the varices below will be obtained as with the tourniquet at this level. In nine patients five good positive tests have been obtained and in two, pressure with one finger combined with "weight-bearing leg swinging" caused complete emptying below the compressed vein. Subsequent operation revealed an incompetent perforator at this point.

7. *Coughing Impulse Test*.—Adams (1939) pointed out the importance of straining pressures in varicose veins stating: "We have felt that the Trendelenburg test, as usually performed is not a satisfactory test of valvular competence, inasmuch as it considers standing pressures only." He observed patients whose valves were competent to standing pressures and so exhibited a normal Trendelenburg, yet whose valves were incompetent to the added pressure of straining and promptly exhibited an abnormal Trendelenburg when this factor was introduced. Consequently Adams speaks of a valve being relatively competent when it stands the ordinary pressures of erect posture but permits reverse flow under the added effect of strain. If the fingers of the palpating hand of the examiner be placed over the saphenous opening of the patient in the standing position, back flow in the incompetent cases is readily detected as a palpable venous thrill when the patient coughs or strains. Adams finally concludes that "pressure and not the reversal of flow is the dilating factor."

Reviews of the pathology of varicose veins and of the physiologic basis of the various tests have been given by Freeman (1939), Ochsner and Mahorner (1939) and Heller (1940).

#### INJECTION TREATMENT

In our series of about 80 patients with varicose veins seen in 1940, only about 5 were advised to have injection alone. About 10 were advised to have ligation, but did not accept operation and the remaining 63 form the basis of this report. Two or three patients with active phlebitis were given palliative treatment.

The injection method was especially popular in the decade 1920 to 1930 when a reaction against the operative treatment occurred. The two chief objections to the injection treatment are the occurrence of reactions and lack of permanency of the method. Reactions have been reported by Kettel (1931), Ritchie (1933), Zimmerman (1934), Praver and Becker (1935), Lewis (1936), Dale (1937), McCastor and McCastor (1937), Shelley (1939), Holland (1939), Kadin (1940), and others. The use of injections is especially supported at the present time by the dermatologists, such as Isaak (1939, 1940). Writing in the former

year, this author stated "today it cannot be denied that the treatment of varicose veins by injections has almost replaced surgical methods." A view in opposition to this was taken by Dean and Dulin (1940) and one of us (H. N. II., 1940).

The old thrombogenic type of injections has been largely replaced by the sclerogenic type. Sodium morrhuate has been used exclusively in our series with no reactions. We have since had one transient reaction in a case not included in this series.

Sodium morrhuate was first used as an injection treatment for varicose veins by Higgins and Kittel (1930), who reported favorably on its use in 187 patients treated at the Royal Northern Hospital, London. Barber (1930) used this method shortly afterward. Ritchie (1933), of Edinburgh, used this method in a large series of cases of pregnancy and about this time sodium morrhuate became popular in the United States.

We have always tried to allow no more than seven days to elapse between large injections. If the patient stays away longer than seven days, the series is begun over again with an initial small (1 c.c. or less) desensitizing dose. This practice was based on the principle that anaphylactic sensitivity usually takes longer than seven to ten days to develop. Holland's (1939) 3 cases of reaction to sodium morrhuate all occurred in patients who had had previous injections of the substance, but in whom an interval of four weeks or more was allowed to elapse before giving a 2 c.c. dose. Ritchie's (1933) case with reaction followed an injection of 2 c.c. given ten days after a first injection.

Only 1 case was treated by the method of segmental sclerosis (injection of sodium morrhuate into the distal cut end of the saphenous vein through a long ureteral catheter) as advised by Pratt (1939). The results in this 1 case were good. We have had no experience with the twin injection technique of Maingot for vein injection as described by Scott (1930) and Fowle (1940).

Because of failures with injection alone in previous cases, we have used operative methods in most of our cases seen in 1940. In general, injection alone was reserved for cases with (1) no palpable superficial veins above the knee and (2) a normal Trendelenburg reaction. With regard to the first criterion it is of interest that Mårtensson (1938) found that relapses developed in all his cases (55 in all) in which the insufficiencies of the veins extended above the lower third of the thigh. Ochsner and Mahorner (1937) reported a 57 per cent recurrence rate following injection alone while other writers reported rates all the way from 0 to 98 per cent.

Much of the benefits of injection so far as a low mortality from embolism are concerned may be attributed to the fact that injections are given to ambulatory patients while operations, at least before 1930, were done on bed patients. Westerborn (1936-37) reported the inci-



dence of fatal pulmonary embolism following different methods of vein treatment in Sweden as follows:

1. *Operation*, 0.26 per cent (6,994 cases operated upon from 1921 to 1925 with 18 deaths from embolism).

2. *Injection plus operation*, 0.33 per cent (1,200 cases treated with 4 deaths from 1928 to 1934).

3. *Injection*, 0.036 per cent (30,000 treated cases with 11 deaths from 1927 to 1934).

It is to be noted that the operation series was all done before 1925, and hence when bed rest for several days afterward was the rule.

*Postoperative Injections.*—In our series of 63 patients, 28 received postoperative injections and the average number of injections per case was 4.7. Slevin (1940) reported that in his series of 73 patients injected after vein ligation, 494 injections were given, an average of 6.76 per patient. Dean and Dulin (1940) opposed injection therapy without preliminary high ligation. In 600 cases treated at the University of Iowa by injection alone, there were 2 deaths from pulmonary embolism. These authors adopted the method of using injections only after high ligation. Taylor (1940) also advised injection only after preliminary ligation.

Our technique of injection postoperatively is to wait about ten days before giving an initial desensitizing dose of 0.5 to 1.0 c.c. of 5 per cent sodium morrhuate. An interval of no longer than a week is then allowed, otherwise the series is begun over with a new desensitizing dose. The dosage is worked up to, but never exceeds 5 c.c. In large veins, we use what we call the "elastoplast technique" of injection. A piece of elastoplast four inches by six inches is slit vertically for 2 cm. in its center. It is then spread tight over the site of injection, the slit now forming an oval opening through which the injection can be given. All patients rest horizontally for twenty minutes after injection and then walk away from the clinic.

*Injection at Time of Operation.*—Only 3 patients in our series received injections into the distal end of a cut vein at the time of operation. Two of these were done by the usual syringe and needle method, while the other was treated with the ureteral catheter technique of Pratt (1939). The results in this latter case were good. These 3 cases were early in the series and since then this method has been abandoned for four reasons:

1. The pain of the injection is far worse than that of the operation and is apt to cause the patients to go to bed with consequent danger of embolism.

2. Injection into a distal segment is not effective unless large amounts of sodium morrhuate are used (e.g., 5 c.c.). If these are used as an initial dose, a reaction may occur. If the patient is desensitized previous to operation, inflammation of the vein may make the operation difficult.

3. Secondary incisions low down on the thigh and on the leg cannot be made after distal injections, as otherwise the injected fluid will leak into these lower wounds.

4. If time is allowed to elapse for the veins to collapse, less fluid need be injected later.

Hawkes and Hewson (1940) also do not inject at the same time as they ligate. They stated that following ligation the veins usually collapse, so that by waiting two weeks they are dealing with a smaller vein and a smaller thrombus will be formed. In patients with bilateral veins, they injected one at the time of operation and allowed a wait of two weeks before injection with the other. The ultimate cosmetic result averaged better where the injection followed a period of waiting. These authors also point out the second objection to injecting at the time of operation; namely, that it may cause so much pain as to necessitate bed rest.

#### OPERATIVE TREATMENT

Operative procedures on varicose veins may be listed in outline form as follows (complete references in Ochsner and Mahorner):

##### A. Before Modern Injection Period.

1. Puncture (Hippocrates, 500 B.C.).
2. Tearing with hook (Galen, 201).
3. Double ligation and section in thigh (Paulus Aegineta, 690), (Paré, 1590). (Trendelenburg, 1890).
4. Removal by dissection (Albucasis, 1106), (Madelung, 1884).
5. Percutaneous ligation (Davat, 1937).
6. Multiple ligations and sections (Schede, 1877).
7. Circular incision.
  - a. Single (Peterson, 1893).
  - b. Multiple (Rindfleisch-Friedel, 1908).\*
8. Stripping.
  - a. Internal wire (Keller, 1905).
  - b. External stripper (C. H. Mayo, 1906).
  - c. Internal stripper (Babcock, 1907).

##### B. After Modern Injection Period.

1. High ligation at fossa ovalis (Homans, 1916).
2. Similar high ligation as ambulatory procedure (de Takats, 1930).
3. High ligation plus retrograde injection.
4. High ligation plus conservative excision at site of incompetent perforators (Homans, 1916).
5. High ligation plus conservative excision or stripping at site of incompetent perforators (Harkins and Schug, 1941).

\*This method is, according to Ochsner and Mahorner (1939), "one of the most atrocious crimes a heavy-handed surgeon ever inflicted on his patients." After excision in the thigh, a circular incision, beginning at the knee and ending at the ankle is passed around the calf four to seven times. The ultimate result looks like a cut rubber tree trunk.

*Importance of Ambulatory Treatment.*—The two periods listed separately above might also be termed the "postoperative bed rest" period and the "ambulatory" period. High mortality from embolism caused the early operative methods to be discredited. Bernitsen (1927), in discussing the results of extirpation of varices in 376 patients, reported embolism in 7.2 per cent and a mortality rate of 0.7 per cent. All of these patients were operated upon before de Takats (1930) introduced operation as an ambulatory procedure. Dean and Dulin (1940) and others stress the importance of ambulatory treatment in these cases.

The operation of high ligation of the saphenous vein as an ambulatory procedure was described by de Takats (1930), who reported 50 such operations. In 1933, de Takats and Quillin reported 150 additional cases, making a total of 200 with 1 death from sepsis. No case of embolism occurred and de Takats and Quillin concluded that "two factors, namely, the ambulatory management and the shortness of the proximal stump, are important in the prevention of embolism." The additional technical point of ambulatory treatment, we believe, has altered the entire results of operative management of varicose veins. The results as far as embolism is concerned have been so good that nine years after de Takats' original paper on the subject, Ochsner and Mahorner (1939) stated that no deaths from this cause following operation "have been reported when ambulatory regimen has been used."

*Multiple Supplementary Ligations.*—It was soon found that multiple ligations were not effective unless a high ligation was performed at the fossa ovalis with division of all the branches of the saphenous vein at this point. Similarly, more recent authors have found that in cases with additional leaks below the fossa ovalis, additional incisions must be made. It is our policy always to ligate at the fossa ovalis, and often to supplement this procedure with additional ligations below. Thus, these multiple ligations below are always supplementary to the fossa ovalis ligation. Essentially this procedure has been advised by Homans (1916), Ochsner and Mahorner (1939), Wright (1940), Rees (1940), and many others. Hawkes and Hewson (1940) do a "two-point" ligation, high and at the site of the lowest perforator. It seems to us that this may not be adequate and that an excision of the vein to eliminate some of the perforators between may be advisable. Slevin (1940) reported that following high ligation alone, he had a recurrence rate of 17 per cent, while with multiple ligations it was only 4 per cent. He mentions, however, that in some of the earlier cases of high ligation, all of the branches of the saphenous vein at the fossa ovalis were not ligated.

Vaughn (1940) stated that he had never done a bilateral ligation as one operative procedure. In our series, 35 of 63 patients (56 per cent) had bilateral ligations performed at one sitting and nothing that occurred in this experience would cause us to abandon treatment of both legs simultaneously.

*The Lesser Saphenous Vein.*—Many authors such as Wright (1940) have written vaguely about the importance of the lesser saphenous vein in causing varicose veins. Few statistics on this subject are available. Slevin (1940) reported that of 100 extremities ligated, in 5 instances (5 per cent) the lesser saphenous was ligated. Slevin also mentions that the lesser and greater saphenous often communicate. In our series of 98 legs, only three definitely enlarged lesser saphenous veins were operated upon (an incidence of 3 per cent). In all other cases it was searched for in the popliteal fossa by inspection and palpation and in seven instances the popliteal fossa appeared so suspicious that an incision was made which revealed no enlarged vein. In the cases where a definite vein was found, however, it was quite large (8 mm. or more) in diameter, but smaller than the vein shown in Fig. 5 of Adams' article (1940), and definitely perforated the deep fascia. Furthermore, intentional release of a clamp on the central end revealed marked bleeding.

Adams (1940) stated that with one exception, he had "not observed any cases of varicosities involving the short saphenous veins in which a definite communication with the long saphenous was not present and we are of the opinion that this rather than the deep femoral vein is the usual mode of transmission of pressure to the short saphenous system." We can agree with Adams in his anatomic observation, but not in his physiologic conclusion. In most cases the lesser saphenous forms the lateral branch of a Y, the medial branch arching from above and anteriorly over the medial condyle of the femur from the greater saphenous. The two unite and go down the back of the calf, the united vein soon branching itself. However, as stated above, in cases of enlarged lesser saphenous veins, we have found a marked flow of blood to come from the central end and in no case have we found valves closer than 3 cm. from the perforation through the fascia.

#### OPERATIVE TECHNIQUE

1. *Hospitalization.*—Of the 63 patients, operation was performed on 62 in the operating room and on 1 in the outpatient clinic. This latter patient developed a hematoma at the fossa ovalis incision. While we believe this operation can be done in an outpatient clinic, we advise that it be done in an operating room. On the other hand, of the 63 patients, 51 were operated upon as outpatients. Of the 12 remaining, 2 were already in the hospital, 1 entered voluntarily before operation, and 5 entered after operation because of their condition (bleeding, prolonged operation, faintness, general anesthesia, etc.). The other 4 patients that entered the hospital did so for economic reasons to obtain hospital and medical insurance to which an outpatient visit would not have entitled them.

2. *Anesthesia.*—All but 1 patient was operated upon under local anesthesia. This 1 patient was an extremely excitable woman of whom

an exception had to be made. Within a few hours after operation, however, she was forced to walk just as though she had been operated upon under local anesthesia. One-half per cent novocain without adrenalin was used in practically all the local cases. No preoperative sedation was used in most of them as it was noted that after using opiates, the patients were apt to faint on adopting the ambulatory regimen. Furthermore, because of traffic dangers, the use of opiates was contraindicated in the outpatients.

3. *Draping and Skin Preparation.*—If only fossa ovalis incisions were to be made, these could be done on both sides at one draping. Otherwise one leg at a time was draped and completed. Iodine was used as it did not wash off the gentian violet markings on the legs that were placed to indicate the site of incisions. An aqueous antiseptic (hexylchloro-M-cresol) was applied in the region of the genitals to avoid burning.

4. *Silk.*—Fine black silk was used in all cases for sutures and ligatures except of the central stump of the saphenous vein where a heavy ligature was used.

5. *Fossa Ovalis Incision.*—We tried the longitudinal incision advised by Ochsner and Mahorner (1939) but have come back again to the oblique incision. The longitudinal incision does not follow the lines of force; it bleeds more easily and is more apt to give rise to a subsequent hematoma; the medial flap tends to pull upward in the middle and the resultant scar is more marked even when approximation is guided by preoperative skin scratches. At the fossa ovalis we now use an obliquely transverse incision a fingerbreadth below and parallel to the femoral crease. Use of the palpated femoral pulse as the lateral end of the incision seems to be a better guide than marking the varix, which often is not visible, in the erect position. Especially in obese patients, as soon as they lie down, the relation of skin to deep tissues becomes distorted and the marks are apt to be misleading. As any medical student knows, however, the femoral artery lies just lateral to the vein and therefore to the fossa ovalis. The vein is found and identified. We have several guides to the vein other than experience. It is usually marked by the typical branches and it lies in the superficial fatty tissues while the femoral vein is at the same depth as the artery which can be palpated. In cases of doubt we lightly pinch the vein to note if the distal segment swells as it would if it were the femoral. Finally, except in cases of visible varices which are superficial, the vein is often much thicker walled than the femoral. At the most accessible point the vein is divided between clamps; the assistant then retracts only the lower margin of the wound, a little novocain is placed along each side of the vein and with a Mayo vein clamp the lower segment is followed down for about two inches in hopes of finding the descending femoral branch. If this is found, it and the vein are separately transfixed and the two-inch segment removed. Otherwise the

saphenous alone is so treated. The assistant then retracts only the upper margin of the wound and the lower stump is forgotten. The upper stump of the vein is followed up to where it enters the fossa ovalis, the lower border of which is marked in about 90 per cent of the cases by the visibly pulsating archlike superficial external pudendal artery. We have found that this technique of dividing the vein at the start of the operation renders exposure of the fossa ovalis much easier than the method of not cutting the vein until the end of the procedure. All branches are doubly clamped and ligated, attempting in all cases to get the three main ones (external pudendal, inferior epigastric, and circumflex iliac). In women the external pudendal often assumes great proportions and should be followed medially until it branches, ligating the two branches separately. The various anomalies at the region of the fossa ovalis which should be searched for and ligated have been pointed out by Stalker and Heyerdale (1940). The saphenous itself is then held up under only moderate tension and ligated even with the edges of the fossa with heavy silk. A fine silk transfixion suture is then placed just distal to the ligature so that no silk crosses the lumen of the proximal portion of the vein. The free portion of the proximal stump is then cut off distal to the transfixion suture. Fine silk is used for all ligatures and sutures except the one most proximal on the stump of the saphenous. In tying it, if too much pull is exerted on the vessel, the same error may be made as occurs in tying off a cystic duct under too much tension; i.e., looping up the femoral vein itself into the ligature as may be done with the common duct. The advisability of leaving a short stump is at once apparent. Kilbourne (1934) stated that high ligation "may cause a funnel-shaped blind pocket in the vein proximal to the ligature in which the blood stagnates allowing a thrombus to form." He stated that ligation has a mortality of 0.5 per cent but cited Schiassi who claimed 2,500 ligations without embolism.

A single silk suture is placed at the midpoint of the deep layer of the superficial fascia and the skin closed with interrupted silk. In these ambulatory patients we have found that end-on mattress sutures are the only ones that will hold the skin edges in approximation at all satisfactorily.

6. *Lower Incisions.*—These are made longitudinally except where they are to allow exit for the end of the stripper, in which case they are horizontal and only 1 cm. long. These incisions are made on the lines previously marked by gentian violet where incompetent perforators are suspected. The most usual site is over the adductor tubercle of the femur. It may be because the femoral vein has at this point just escaped from Hunter's canal that it so often gives a large perforating branch in this region. All branches are ligated and the main saphenous vein as high as possible at the upper end of the incision and as low as possible at the lower end is transfixed. A suture is inserted subcutaneously every 2 cm. to approximate the fascia and the wound closed with skin silk.

In our series, 217 incisions were made on 98 legs. On all but 1 leg, a fossa ovalis incision was made, so this made 120 incisions below the groin, an average of 1.3 per leg. We believe that a fossa ovalis incision and accompanying ligation should be done on every case where any operation is performed. We did not do it on this 1 leg (the second leg of a bilateral operation) because of the length of the operation. Only 28 patients had only fossa ovalis incisions and it is of interest to note that these all were during the first half of the period covered by this report. Thirty-one incisions were made below the knee (13 per cent of the total) and of these 29 were done during the second half of the series. It is thus seen that so far as operating below the groin and below the knee is concerned, we became much more radical as time went on.

7. *Stripping*.—When we began stripping as an ambulatory procedure, we were told that it was not feasible because of pain and hemorrhage. Neither of these fears was justified. Simple novocainization just under the skin is adequate for a practically painless stripping if the course of the vein has been accurately marked ahead of time. Furthermore, with elastoplast, no case of hemorrhage or hematoma occurred. We have, however, abandoned stripping the proximal six inches of the saphenous vein because the elastoplast cannot exert pressure at this level and one hemorrhage occurred above the compression. A Mayo vein stripper is used in all cases and with practice when a branch is reached it is identified, the stripper cut down upon, the branch doubly ligated and the stripping proceeded with. Even when a branch is torn, however, no hematoma has resulted with elastoplast. Visible veins are usually friable or attached firmly to the dermis and unsuitable for stripping. Finally, recent previous injections may cause stripping to be difficult. Otherwise, we substitute stripping for excision as much as possible as the cosmetic result is better. We have repeatedly noted that if a segment of vein is left behind between ligations, it becomes much more painful than the channel left by stripping such a vein. Nineteen patients had stripping, 15 of them during the second half of the series. Most stripping was done in the lower thigh and seldom below the upper fourth of the leg.

8. *Dressings*.—We have found that an extremely small piece of gauze, 1 by 3 inches, covered by a 2 by 6 inch piece of adhesive tape is much less apt to lead to infection of the fossa ovalis incision than bulkier dressings. The skin is always rubbed beforehand with ether to cause the adhesive to stick well. The lower incisions are dressed with small pieces of gauze and a roll of elastoplast from two inches below the lowest incision to two inches above the uppermost one.

9. *Postoperative Orders*.—Prime emphasis is placed on frequent walking and nothing is done to interfere with this. Consequently only aspirin is given as an analgesic. In fact, now that we do not use

injections at the time of operation, pain is not an important factor. All patients who had had injections sometime before operation stated that the operation hurt far less than an effective injection. The patients are informed of the "seven-hour rule": that they must not stay in bed longer than seven hours at one time for several weeks. If they wish to go to bed early and get up late, they must get up once in the middle of the night. They are not cautioned against standing, for fear that this will cause them to rest and also in the sincere belief that if they have been improved by the operation, that improvement begins at the time of operation and reversed blood flow on standing will no longer be a factor. The dressing is usually changed on the sixth day, and at that time one-third of the stitches are removed, the remaining coming out on the eleventh day, at which time postoperative injections may be begun if necessary.

#### ANALYSIS OF MATERIAL

This study consists of an analysis of operations of 98 separate lower extremities done on 63 individuals during a one-year period between Jan. 13, 1940, and Jan. 12, 1941. All procedures and operations were done by the senior author (H. N. H.) except 3, which were under his direct supervision. Forty-two of these patients have been rechecked in the past six weeks (Jan. 1, 1941, to Feb. 15, 1941) to determine the present condition of their veins and the status of their legs, as well as to obtain their own estimation of improvement or other alteration of their condition. Twenty-one patients were not contacted. This was probably due to the fact that some of the patients only lived or worked in Detroit for a short time and also to the fact that many of our patients came from some distance outside of the city. In the latter group we were able to get an approximate appraisal of results through correspondence.

The longest we have been able to follow any of these cases is 13½ months. Because of this a final conclusion cannot be drawn; however, we believe that the results obtained by our treatment merit presentation at this time.

TABLE I

#### VARICOSE VEIN SURVEY

(TOTAL NO. CASES, 63; NO. LOWER EXTREMITIES OPERATED UPON, 42)

SEX INCIDENCE		SIDE INCIDENCE	
Males	28	Left leg	56
Females	35	Right leg	42

*Scr.*—The group included 35 women and 28 men. Ochsner and Mahorner (1937) observed 247 women and 38 men, and Hawkes and Hewson (1940), 441 women and 159 men, so a preponderance of females seems to be the rule. The excess was less in our series in all probability because of the industrial nature of our clientele.



In our series, 217 incisions were made on 98 legs. On all but 1 leg, a fossa ovalis incision was made, so this made 120 incisions below the groin, an average of 1.3 per leg. We believe that a fossa ovalis incision and accompanying ligation should be done on every case where any operation is performed. We did not do it on this 1 leg (the second leg of a bilateral operation) because of the length of the operation. Only 28 patients had only fossa ovalis incisions and it is of interest to note that these all were during the first half of the period covered by this report. Thirty-one incisions were made below the knee (13 per cent of the total) and of these 29 were done during the second half of the series. It is thus seen that so far as operating below the groin and below the knee is concerned, we became much more radical as time went on.

7. *Stripping*.—When we began stripping as an ambulatory procedure, we were told that it was not feasible because of pain and hemorrhage. Neither of these fears was justified. Simple novocainization just under the skin is adequate for a practically painless stripping if the course of the vein has been accurately marked ahead of time. Furthermore, with elastoplast, no case of hemorrhage or hematoma occurred. We have, however, abandoned stripping the proximal six inches of the saphenous vein because the elastoplast cannot exert pressure at this level and one hemorrhage occurred above the compression. A Mayo vein stripper is used in all cases and with practice when a branch is reached it is identified, the stripper cut down upon, the branch doubly ligated and the stripping proceeded with. Even when a branch is torn, however, no hematoma has resulted with elastoplast. Visible veins are usually friable or attached firmly to the dermis and unsuitable for stripping. Finally, recent previous injections may cause stripping to be difficult. Otherwise, we substitute stripping for excision as much as possible as the cosmetic result is better. We have repeatedly noted that if a segment of vein is left behind between ligations, it becomes much more painful than the channel left by stripping such a vein. Nineteen patients had stripping, 15 of them during the second half of the series. Most stripping was done in the lower thigh and seldom below the upper fourth of the leg.

8. *Dressings*.—We have found that an extremely small piece of gauze, 1 by 3 inches, covered by a 2 by 6 inch piece of adhesive tape is much less apt to lead to infection of the fossa ovalis incision than bulkier dressings. The skin is always rubbed beforehand with ether to cause the adhesive to stick well. The lower incisions are dressed with small pieces of gauze and a roll of elastoplast from two inches below the lowest incision to two inches above the uppermost one.

9. *Postoperative Orders*.—Prime emphasis is placed on frequent walking and nothing is done to interfere with this. Consequently only aspirin is given as an analgesic. In fact, now that we do not use

*Duration of Symptoms.*—In 46 cases analyzed, the average duration of symptoms was 16.3 years.

*Symptoms.*—The three main symptoms were pain, swelling, and disfigurement as shown in Table III. The number of patients who had no other complaint than the appearance of the veins is surprising. Other symptoms did not always seem to be proportionate to the size of the veins.

*Previous Injections.*—Twenty-one patients had had previous injections, the average being 13.7 per patient.

TABLE IV  
VARICOSE VEIN SURVEY  
MODE OF ONSET OF SYMPTOMS (43 CASES)

Gradual	30
Gradual with pregnancy	3
Acute	10
With milk leg at pregnancy	2
With pregnancy alone	3
With thrombophlebitis after surgery	2
With ulcer, pain, or swelling	3

TABLE V  
VARICOSE VEIN SURVEY  
PREVIOUS TREATMENT (63 CASES)

SURGERY			INJECTIONS	
NO.	PLACE	DATE	No. of patients injected	21
1	H. F. H.*	1935	Average no. injections per patient	13.8
2	H. F. H.	1939	<i>Other methods of treatment:</i> 1. Elastic stockings 2. Ace bandages 3. Soocy and Unna paste boots 4. Salves, ointments, pastes	
2	Outside	1938		
1	Outside	1930		
1	Outside	Unknown		
Total	7 cases			

\*Henry Ford Hospital.

*Previous Operations.*—Seven patients had had previous unsuccessful vein operations. Three of these were done in our own hospital and 4 elsewhere. In some instances it was difficult to tell what had been done previously, while in others the findings were extremely interesting. In 1 case one limb of a bifid saphenous had been ligated below the fossa ovalis. In another, the vein had recanalized after ligation. In another, a lesser saphenous had been overlooked. The most interesting case, however, and most recently operated upon was that done by an assistant resident in 1939. Dissection revealed that he had ligated the external pudendal where it entered the saphenous, evidently mistaking this point for the saphenofemoral junction. The ligature was still in place!

In our own series 1 reoperation was done (a lesser saphenous overlooked previously in one of our early cases), and 1 other was advised (an evident perforator near the adductor tubercle in one of our early cases).

*Age.*—By far the largest proportion (63 per cent) of the patients was between the ages of 40 to 54 years, thus possibly lending support to Sicaud's (1929) hormonal theory. It is more probable, however, that employment, economic factors, and progression of the disease played a role in causing persons of this age to seek attention. Hawkes and Hewson (1940) found a slightly smaller number to fall in this age group, 45 per cent of their patients being within the age group of 40 to 59 years.

*Side.*—The left leg was involved in 56 instances and the right in 42. On the right leg 125 incisions were made and on the left 92. Ochsner and Mahorner (1939) stated that neither side was involved more, while Stenbner (1930), cited by Ochsner and Mahorner, found the right leg to be involved slightly more often, the opposite to our series. We operated upon 38 of 63 patients (60 per cent) bilaterally while Hawkes and Hewson (1940) operated upon 440 of 600 patients (76 per cent) bilaterally. An economic factor may have caused our percentage to be low.

TABLE II  
VARICOSE VEIN SURVEY

AGE INCIDENCE (62 CASES)		DURATION OF SYMPTOMS (46 CASES)	
20-24 yr.	2	0-4 yr.	2
25-29 yr.	2	5-8 yr.	11
30-34 yr.	5	9-12 yr.	3
35-39 yr.	1	13-18 yr.	8
40-44 yr.	14	19-24 yr.	8
45-49 yr.	15	25-35 yr.	10
50-54 yr.	11	36-45 yr.	3
55-59 yr.	5	46-55 yr.	1
60-64 yr.	3	Average	16.3 yr.
65-70 yr.	4		

TABLE III  
VARICOSE VEIN SURVEY

	0	±	+	++	+++	++++*
<i>Severity of presenting symptoms (42 cases):</i>						
Pain	8	2	11	6	8	6
Swelling	5	0	8	14	8	6
Appearance	18	1	9	7	6	0
No. of cases of ulcer	22					
<i>Postoperative severity of symptoms (42 cases):</i>						
Pain	30	7	2	3	0	0
Swelling	26	10	6	0	2	0
Appearance	36	2	2	2	0	0
No. of ulcers present Feb. 21, 1941	2					

\*These notations refer to the intensity of the symptoms: 0, absent; ±, trace; +, mild; ++, moderate; +++, marked; and +++, severe.

*Mode of Onset.*—The onset was gradual in 30 cases, gradual with pregnancy in 3 more cases, and acute in 10 cases (2 of these cases occurred with milk-leg at pregnancy, 2 without milk-leg at pregnancy, 2 with thrombophlebitis following abdominal operation, and 3 were acute with ulcer, pain, or swelling).

the instances of silkosis, what might be called a dry silkosis was present. In no case was there infection or moistness except within a millimeter of the extruded stitch and at no place did more than one stitch come out. In conclusion, therefore, in our hands infection after operation has played a minor role in varicose vein surgery even though as Freeman (1939) has pointed out "the groin is a susceptible spot for infection." Also, like Freeman, "we have used silk in all of our operations and have had no cause to regret it."

*Keloid*.—A small nonpainful keloid formed in 1 case.

*Hemorrhage*.—Hemorrhage occurred in 6 cases, all during the first eight months of the year covered by this report. Four hemorrhages occurred at the fossa ovalis, all in cases done before we adopted transfixion suture of both ends of the main vein. One was in the one patient done in an outpatient office, 1 was in a secondary operation following recurrence, and the other 2 were in simple cases, except that in 1 of them, Case C. S., a lymph gland overlay the saphenous vein. The presence of a lymph gland in this position has, we have found, doubled the difficulty of the operation. The other 2 occurred lower down. One was in our first operation near the knee which was done before we used elastoplast. The other was our first and only attempt to strip the entire saphenous from fossa ovalis to just below the knee on an ambulatory patient. Bleeding occurred high in the thigh above the level of the elastoplast. Two patients had to have the wounds reopened at the fossa ovalis and one at the knee. We believe that following three rules would have prevented all these hemorrhages: (1) Use of transfixion sutures on all main vessel stumps, (2) avoidance of stripping the upper thigh, and (3) the use of elastoplast.

*Lymph Drainage*.—In our series there were 3 patients with some persistent pain after operation; there were 2 in whom swelling of the leg was a little worse (there was no swelling of the foot or ankle in these cases), and there were several, chiefly those in whom the prescribed course of postoperative injections was never completed, in whom visible but asymptomatic veins persisted. We had no patients in whom the veins seem to be growing larger again. In a few instances spider bursts occurred some weeks after operation.

Our one bad result, however, was in Patient C. S., male, aged 54 years, operated upon June 22, 1940, for veins of eight years' duration, much worse on the right. A bilateral excision and ligation at the fossa ovalis was done and the right leg, previously the worse of the two, was an excellent result. Hemorrhage occurred, however, at the left fossa ovalis, an assistant reopened the wound and ligated a bleeding point. The operation on this side had not been unusual except that a large adherent lymph gland overlay the saphenous vein. Infection occurred which was followed by lymph drainage for three months before the wound finally healed. For a time the lymph secretion was so marked that several hundred cubic centimeters drained off in a day.

*Stitch Infections.*—These occurred in 9 cases but were healed in all cases within seven days or less, except in 1 and that was healed within three weeks. In labeling these cases as infections, we used the strictest possible interpretation of the word and included all instances that did not heal 100 per cent primarily. Even if the wound edges healed primarily but yet the stitch holes exuded a drop of pus or fluid, the case was called an infection.

*Infected Wounds.*—Only two deep infections occurred and both of these followed hematomas and were well localized. Both of these occurred during the first half of the series and since during the second half we adopted better measures to prevent hematomas, we believe that infection is no longer an important factor. Both infected wounds healed without extruding the silk ligatures.

*Seroma.*—Only two wounds developed a seroma and both of these healed promptly after evacuation.

*Silkosis.*—\*Only 3 wounds developed silkosis. Not a single one of the 97 fossa ovalis incisions developed silkosis. All of the instances occurred in cases where the operation was performed during the first two-thirds of the year while we were using more buried sutures to close the dead space in thigh and calf wounds. More latterly when we were using only one such suture for every inch length of incision and relying on elastoplast to obliterate the defect no silkosis occurred. Finally, in

---

\*We define silkosis as the condition where buried silk extrudes from and has to be pulled out of an operative wound.

ligating of a vein before the ulcer is healed, and we feel that we hasten its closing in doing a ligation and by injecting the feeder veins."

Luke (1940) has ligated 58 cases with ulcers with good results. He believes that temporizing should not be carried too far in these cases and that with surgical treatment "the healing of the long-standing ulcers following this procedure is phenomenal." No ulcer took longer than six weeks to heal, but 3 patients returned with recurrence of the ulcer after initial healing in Luke's series.

In our own series, in 63 patients, ulcers were present in 26. Of 42 patients with a recent follow-up, 22 ulcers were present at the time of operation and of these, 2 were still present at the time of making this report. Of these latter, 1 was an ulcer of nineteen years' duration in which a skin graft was advised and refused, while the other ulcer had healed after operation, but recently had broken down again.

*Vitamin B<sub>1</sub>*.—In 5 cases we used vitamin B<sub>1</sub> by mouth to control pain, usually in the presence of ulcer. In 3 cases there was a good result; in 2 there was slight improvement. The periodicity of the pain in this condition makes this result difficult to interpret. We used 30 mg. of thiamine chloride a day which is equal to the maximum dose used by Ochsner and Smith (1940). These authors and Krieg (1938), the introducer of the method, have been its chief advocates.

#### SUMMARY

In a series of varicose vein operations personally conducted on 98 extremities of 63 patients during 1940, 217 incisions and 19 strippings were done.

#### CONCLUSIONS

1. A stereotyped operation should be avoided. The surgical procedure should be individualized to fit the patient and to block all important venous incompetencies as determined by complete diagnostic tests.

2. High ligation and segmental excision of the saphenous vein and all its branches at the fossa ovalis should be performed in all cases submitted to surgery.

3. Additional ligations and excisions lower down on the thigh or leg should be performed as indicated.

4. Stripping gives a better cosmetic result than excision and is preferable to the latter except in cases of superficial, friable, or recently sclerosed veins and for veins high in the thigh.

5. Injection as an adjunct to surgery is best postponed until the second week after operation.

6. Important points in the surgical technique include the use of local anesthetic, silk, transfixion of main vessels, elastoplast bandages, and ambulatory cure in all cases.

7. The one ill effect of consequence in these cases was a slight increase in edema of one leg in two cases and a marked edema in another case.

Since then the patient has had marked edema and pain in this leg, and previously only slightly involved, leg. The edema does not involve the foot but does include the ankle and shin.

#### VARICOSE ULCER

The treatment of varicose ulcers is essentially of two types: that directed toward the ulcer and that directed at improving or curing the causative veins. Of methods directed primarily toward the ulcer, the following are to be noted: (1) bed rest and elevation, (2) rubber sponge dressings (the "venous heart" of McPherson and Merkert, 1931), (3) boots of the Unna or Soocy type,\* (4) elastoplast, and (5) ointments, pastes, and powders. Of the latter, sulfanilamide and aspirin are two of the latest. Our own experience has chiefly been with the Soocy boot, elastoplast, and to some extent with sulfanilamide, zinc stearate, and zinc peroxide powders. Wright (1940) used aspirin powder locally and Gould-Hurst (1940) used histamine iontophoresis. Rees (1940) used sulfanilamide powder locally with success. When these conservative means do not work, skin grafting as advised by Linton (1938), Oelsner and Mahorner (1939), and others is to be used, but in our series of the only 3 patients whose ulcers did not heal promptly with other means 1 refused grafting and the other 2 could not be traced.

The other method of treating ulcers is to treat the accompanying veins. This was done in all cases included in this series. Certain men have stated that ligation should not be done in the presence of an ulcer. They advise waiting until the ulcer is healed before proceeding with the ligation. We believe that this is as wise a doctrine as waiting to ligate a bleeding carotid artery until the patient is in condition to stand it. In fact we have ligated veins in cases in which ulcers had persisted as long as twelve years, conservative therapy being administered all this time by the advocates of this doctrine as a preparation for ligation! We believe, therefore, in accordance with Rees (1940) and Luke (1940), Hawkes and Hewson (1940) and many other recent writers that in cases of varicose ulcer ligation should be done to cure the ulcer. Of course, in the presence of acute inflammation, a few weeks' preparative treatment is wise. Furthermore, in ulcer cases, if tests indicate the necessity for multiple ligations down as far as just above the ulcer, only the upper ligations should be done as a first-stage operation. Then later, if and when the ulcer has healed, persistent incompetent veins near it can be ligated or excised.

Hawkes and Hewson (1940) stated in this regard: "It is remarkable to see how quickly the pain will be relieved in an ulcer following ligation. We have seen no untoward complications develop from the

\*The Soocy boot which is used at the Henry Ford Hospital, differs from the Unna paste boot chiefly in its phenol content

32. Ochsner, A., and Smith, M. C.: The Use of Vitamin B<sub>1</sub> for the Relief of Pain in Varicose Ulcers, *J. A. M. A.* 114: 947-948, 1940.
33. Pratt, G. H.: Surgical Treatment of Varicose Veins and Ulcers by Segmental Sclerosis: With a Discussion of the Effect on Peripheral Arterial Disease and the General Circulation, *Am. J. Surg.* 44: 31-38, 1939.
34. Pratt, G. H.: Segmental Sclerosis of the Saphenous Vein for Varicose Veins, Ulcers and Diminished Arterial Supply, *J. A. M. A.* 113: 925-927, 1939.
35. Pratt, G. H.: Surgical Considerations in the Treatment of Chronic Lymphedema and of Varicose Veins, *Bull. New York Acad. Med.* 16: 381-388, 1940.
36. Praver, L. L., and Becker, S. W.: Sensitization Phenomena Following the Use of Sodium Morrhuate for the Chemical Obliteration of Varicose Veins, *J. A. M. A.* 104: 997, 1935.
37. Rees, H. C.: Varicose Ulcers: The Newer Methods of Treatment, *J. Michigan M. Soc.* 39: 936-938, 1940.
38. Ritchie, A.: The Treatment of Varicose Veins During Pregnancy, *Edinburgh M. J.* 40: 157-164, 1933.
39. Schiassi: Cited by Kilbourne (1934).<sup>20</sup>
40. Scott, N.: The Treatment of Varicose Veins by Injection, *Brit. M. J.* 2: 58-59, 1940.
41. Shelley, H. J.: Allergic Manifestations With Injection Treatment of Varicose Veins: Death Following an Injection of Monoethanolamine Oleate (Mono-oleate), *J. A. M. A.* 112: 1792-1794, 1939.
42. Sicard, J. A., and Gaugier, L.: *Le traitement des varices par les injections locales sclerosantes*, Paris, 1929, Masson et Cie.
43. Slevin, J. G.: Varicose Veins: Surgical Treatment of 100 Cases Analyzed, *J. Michigan M. Soc.* 39: 932-936, 1940.
44. Stalker, L. K., and Heyerdale, W. W.: Factors in Recurrence of Varicosities Following Treatment, *Proc. Staff Meet., Mayo Clin.* 15: 350-352, 1940.
45. Stalker, L. K., and Heyerdale, W. W.: Factors in Recurrence of Varicosities Following Treatment, *Surg., Gynec. & Obst.* 71: 723-730, 1940.
46. Taylor, K. P. A.: Injection of Varicose Veins, *J. A. M. A.* 114: 2489, 1940.
47. Trendelenburg, F.: Ueber die Unterbindung der Venu saphena magna bei Unterschenkelvaricen, *Beitr. z. klin. Chir.* 7: 195, 1890.
48. Vaughn, A. M.: Varicose Veins, *Illinois M. J.* 78: 137-148, 1940.
49. Westerborn, Anders: Ueber die Emboliegefahr bei Injektionsbehandlung von Varizen nebst einem Bericht über die in Schweden vorgekommenen Emboliefälle, *Acta chir. Scandinav.* 79: 321-358, 1936-1937.
50. Wright, A. Dickson: Treatment of Varicose Veins, *Brit. M. J.* 1: 665-668, 1940.
51. Wright, A. Dickson: Complications of Varicose Veins, *Brit. M. J.* 1: 699-703, 1940.
52. Zimmerman, L. M.: Allergic-Like Reactions From Sodium Morrhuate in Obliteration of Varicose Veins, *J. A. M. A.* 102: 1216-1217, 1934.



## REFERENCES

1. Adams, J. C.: Etiological Factors in Varicose Veins of the Lower Extremities, *Surg., Gynec. & Obst.* 69: 717-727, 1939.
2. Barker, T. H. T.: Intravenous Sclerosing Solution, *Brit. M. J.* 2: 59-60, 1939.
3. Berggren, A.: Des varices du membre inférieur, spécialement au point de vue de l'étiologie et du traitement chirurgical, *Acta chir. Scandinav.* 62: 61-87, 1927.
4. Dale, M. L.: Reaction Due to Injection of Sodium Morrhuate, *J. A. M. A.* 163: 718, 1937.
5. Dean, G. O., and Dudin, J. W.: Treatment of Varicose Veins, *Arch. Surg.* 39: 711-719, 1939.
6. Dean, G. O., and Dudin, J. W.: Pulmonary Embolism Following the Injection Treatment of Varicose Veins, *J. A. M. A.* 111: 1313-1315, 1940.
7. De Takats, G.: Ambulatory Ligation of the Saphenous Vein, *J. A. M. A.* 94: 1191-1197, 1929.
8. De Takats, G.: "Resting Infection," in Varicose Veins: Its Diagnosis and Treatment, *Am. J. M. S.* 184: 57-66, 1932.
9. De Takats, G., and Quillin, L.: Ligation of the Saphenous Vein: A Report of Two Hundred Ambulatory Operations, *Arch. Surg.* 26: 72-88, 1933.
10. Fowler, J. A.: Twin Injection Technique of Varicose Veins, *J. A. M. A.* 114: 272, 1940.
11. Freeman, N. E.: Physiological Principles in the Treatment of Varicose Veins, *S. Clin. North America* 19: 1525-1544, 1939.
12. Gould Hurst, S. V.: Treatment of Varicose Ulcers With Histamine Iontophoresis, *Lancet* 1: 739-740, 1940.
13. Harkins, H. N.: Pulmonary Embolism Following Injection Treatment of Varicose Veins, *J. A. M. A.* 115: 236, 1940.
14. Heller, R. L.: The Pathological Physiology of Varicose Veins: Collective Review, *Internat. Abst. Surg.* 71: 566-571, 1940.
15. Higgins, T. T., and Kettel, P. B.: The Use of Sodium Morrhuate in Treatment of Varicose Veins by Injection, *Lancet* 1: 68-69, 1939.
16. Holland, G. A.: Reactions From Sodium Morrhuate in the Sclerosing of Varicose Veins, *Canad. M. A. J.* 41: 262-263, 1939.
17. Isack, L.: Injection Treatment of Varicose Veins: With and Without High Ligation of the Saphenous Vein, *M. Rec.* 149: 169-170, 1939.
18. Isack, L.: Pulmonary Embolism Following the Injection Treatment of Varicose Veins, *J. A. M. A.* 114: 2139, 1940; 115: 632, 1940.
19. Kettel, K.: Über Todesfälle im Anschluss an die Injektionsbehandlung von Varizen, *Zentralbl. f. Chir.* 58: 1498-1510, 1931.
20. Kilbourne, Norman J.: Elimination of Certain Dangers in the Treatment of Varicose Veins, *Am. J. Surg.* 25: 148-151, 1931.
21. Krieg, E.: Die Beeinflussung des Krampfaderleidens durch Vitamin B., *München. med. Wchnschr.* 85: 9-11, 560-561, 1938.
22. Lewis, K. M.: Anaphylaxis Due to Sodium Morrhuate, *J. A. M. A.* 107: 1298, 1936.
23. Linton, R. R.: New Surgical Technique for Treatment of Postphlebitic Varicose Ulcers of the Lower Leg: Preliminary Report, *New England J. Med.* 219: 367-372, 1938.
24. Luke, Josephus C.: The Etiology and Modern Treatment of Varicose Ulcer, *Canad. M. A. J.* 43: 217-221, 1940.
25. Mårtensson, K.: On the Conditions and Results of Injection-Therapy on Varices and a Clinical-Anatomical Study of the Relapses, *Acta chir. Scandinav.* 81: 237-280, 1938.
26. McCallig, J. J., and Hoyerdale, W. W.: A Basic Understanding of Varicose Veins, *J. A. M. A.* 115: 97-100, 1940.
27. McCastor, J. T., and McCastor, M. C.: Reaction to Sodium Morrhuate Injections for Varicose Veins and Hydrocele, *J. A. M. A.* 109: 1799-1800, 1937.
28. McPheeters, H. D., and Merkert, C. E.: Varicose Ulcers: Treatment With "The Rubber Sponge or Venous Heart" and Supportive Bandage, *Surg., Gynec. & Obst.* 52: 1161-1169, 1931.
29. Ochsner, A., and Mahorner, H. R.: The Modern Treatment of Varicose Veins, *SURGERY* 2: 889-902, 1937.
30. Ochsner, A., and Mahorner, H. R.: The Modern Treatment of Varicose Veins as Indicated by the Comparative Tourniquet Test, *Ann. Surg.* 107: 927-951, 1938.
31. Ochsner, A., and Mahorner, H.: Varicose Veins, St. Louis, 1939, The C. V. Mosby Co.

Normally, the allantois expands to form the primitive bladder, then courses anteriorly to open on the ventral surface of the embryo. The hind-gut is at the level of and posterior to the primitive bladder. Caudad to this region the minute continuation and extremity of the intestinal tract is known as the tail-gut. As early as the third week, the bladder and the hind-gut empty into a common cavity called the cloaca, which is separated from the exterior by the cloacal membrane. In the six-week embryo the urogenital groove is beginning to grow downward and by the seventh week the urogenital and intestinal systems have been partitioned by this groove. The cloacal membrane is then divided into urogenital and anal membranes respectively, and by the eighth week the urogenital membrane breaks down to establish an

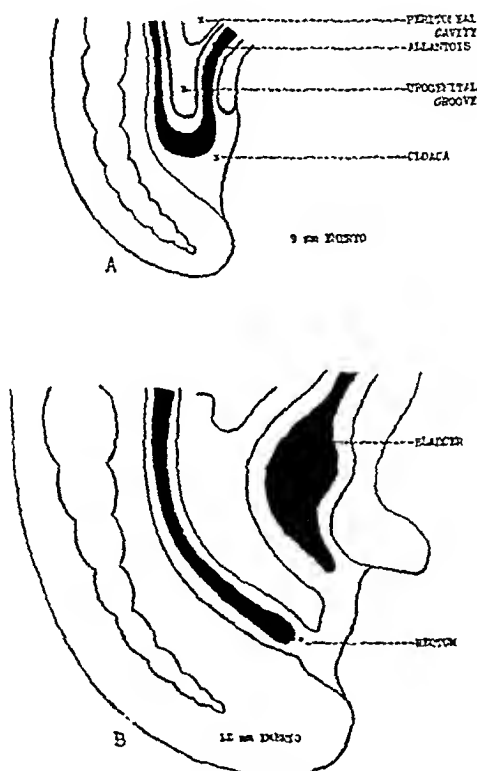


FIG. 1—A. The formation of the cloaca as it exists in the 9 mm embryo. B. The separation of the bladder and rectum in the 12 mm embryo. (After David.)

external opening. In the region of the future anus an invagination develops which is known as the proctodeum. Normally, the anal membrane ruptures during the eighth week to establish continuity between the proctodeum and the anus. Any failure of the anal membrane to break down results in an imperforate anus.

It is apparent that any arrest in the downward growth of the urogenital groove, which should separate the intestinal tract from the urinary system, will result in residual communicating fistulas (Fig. 1).

# CONGENITAL MALFORMATIONS OF THE RECTUM AND ANUS

## AN ANALYSIS OF THE EMBRYOLOGICAL BACKGROUND, TREATMENT AND RESULTS IN 25 PATIENTS

DWIGHT E. HARKEN, M.D., BOSTON, MASS.

*(From the Children's Surgical Service of Bellevue Hospital, New York City)*

**I**N 1858 Henry J. Bigelow, Professor of Surgery at the Harvard Medical School, said: "Judging from results, I do not consider the operation for imperforate rectum or even for imperforate anus, a desirable one. I believe that in the present state of the art it is better that a child born with either of these imperfections should die without this operation; although it must occasionally be performed in deference to established opinion."

The scientific and personal criticisms evoked by this honest statement were almost annihilating. More than eighty years have elapsed since that able man voiced his discouraging counsel. The art has carried on, the technique has been improved and the science has forged ahead at a pace that not even he could have foreseen. Even so, eighty years later, surgeons must fear, at least privately, that he might today utter the same statement.

The volume of isolated case reports in the medical literature is tremendous; however, there are few reports presenting any considerable number of cases. This is due to the fact that while not rare, these conditions are uncommon, occurring but once in every 5,000 to 10,000 births. Unfortunately, the great majority of reports have presented individual malformations of the anus or rectum and their immediate or emergency surgical treatment. It is, therefore, difficult to obtain a fair assay of the end results and almost impossible to evaluate specific types of malformations from the prognostic point of view. In short, it is difficult to know just how right Bigelow still may be.

Our series of twenty-five cases is at once discouraging and gratifying. It has extended over a period of years sufficient that a few facts related to therapy and prognosis in certain types of anomalies are beginning to become apparent. It is with this thought in mind that these cases have been reviewed.

### EMBRYOLOGY

These congenital malformations of the anus and rectum can be best understood when viewed as perversions of embryological development. There are a great many excellent discussions of this aspect of the problem, among these the comments of Lewis,<sup>1</sup> Arcy,<sup>2</sup> Ladd and Gross,<sup>3</sup> and David.<sup>4</sup> Our working concept has been formulated from these sources.

The distribution of our twenty-five cases on the basis of this classification is shown in Table I. It will be observed that there are no malformations of Type I. This finding is in sharp contrast to the figures given in the series of Ladd and Gross, who reported that more than 13 per cent of their cases fell into this group. This may be due to the fact that our cases do not include those treated in the out-patient department. In our experience 86 per cent of the entire series was of Type III; this agrees with other reports from the literature.

TABLE I  
DISTRIBUTION OF FOUR TYPES OF MALFORMATION OF RECTUM AND ANUS,  
WITH AND WITHOUT ASSOCIATED FISTULAS

TYPE	MALES	MALES WITH FISTULAS	FEMALES	FEMALES WITH FISTULAS	TOTAL	TOTAL FISTULAS
I						
II	2				2	
III	13	1	4	3	17	7
IV	6				6	
Totals	21	1	4	3	25	7

Fistulas may be associated with any of the four types of anal or rectal defects. The existence of fistulas, as has been pointed out, is explained by a failure to develop a complete septum between the urogenital and intestinal systems by the partitioning downgrowth of the urogenital groove. It is to be expected, then, that fistulas in the male might be either rectovesical or rectourethral in nature; whereas, in the female the fistulas might be rectovesical, rectourethral, rectouterine, or rectovaginal in type. Actually these embryologically anticipated fistulas are found clinically. The rectovesical and rectourethral fistulas in the female are, however, very rare; the explanation apparently lies in the fact that the Müllerian ducts take over existing partition defects in their downward growth. In the female the low rectovaginal fistula and in the male the rectourethral fistula are much more frequently seen than any other types. The common types are shown in Fig. 2.

In the present series fistulas were found only in Type III cases. Seven patients, or 28 per cent, had fistulas. Of these 7 patients, 4 were males and all presented the common rectourethral communications; of the 3 females, all were found to have the low rectovaginal type of fistulas as shown in Fig. 2.

#### TREATMENT

The treatment of these rectal anomalies is obviously surgical. The extent of this surgical procedure may vary from the inadvertent rupture of a paper-thin rectal or anal membrane, at the time of the postnatal rectal examination, to the most complex reconstructive procedure superimposed upon an original colostomy.

The anal sphincters are derived from mesenchyme and are therefore independent in their development from the ectodermal and entodermal origins of the anus, rectum, and intestine. The probable clinical significance of this fact will be considered in the paragraphs on surgical treatment and in the discussion.

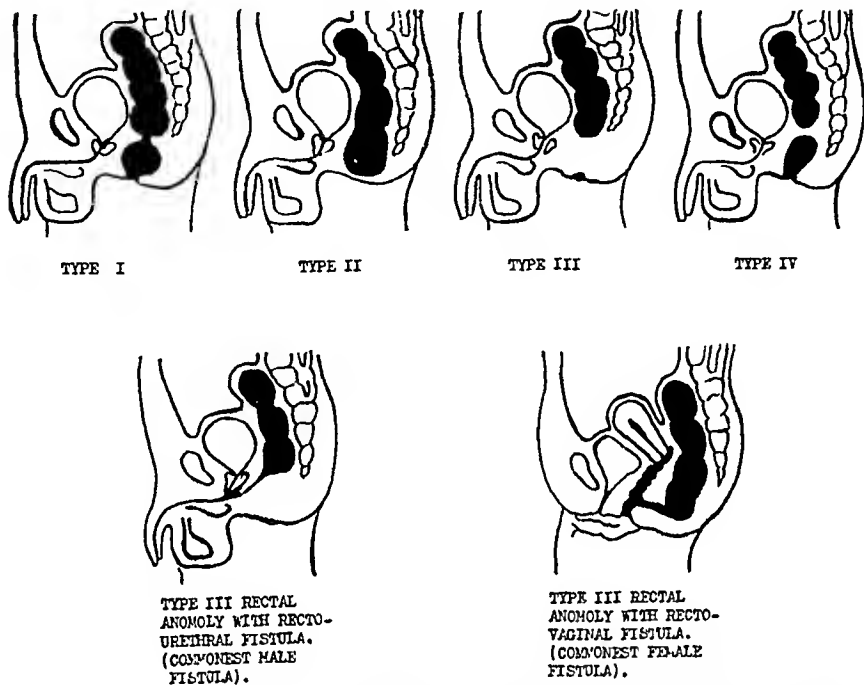


Fig. 2—A classification of anomalies as arranged by Ladd and Gross. *Type I.* Incomplete rupture of the anal membrane or stenosis from 1 to 4 cm above the anus. *Type II.* Imperforate anus, patency interrupted by an anal membrane only. *Type III.* Imperforate anus, also an incomplete rectum, the large intestine ending blindly as a pouch within or above the pelvis. *Type IV.* Apparently normal anus and lower rectal pouch but not communicating with a blind overlying rectal pouch. The two blind pouches may be separated by a thin membrane, or considerable tissue may intervene. Any of the above types may occur in males or females, and in either sex the incidence of fistulas is considerable. The commonest type of anomaly in either sex is *Type III*, the commonest types of fistulas in the two sexes are illustrated above. (After Ladd and Gross.)

#### CLASSIFICATION

The most logical classification available for the consideration of these malformations has been presented by Ladd and Gross,<sup>3</sup> and more recently reviewed by Berman.<sup>5</sup> Ladd and Gross divide these rectal and anal malformations into four types (Fig. 2). Types I and II are easily explained on the basis of the embryological concepts described above. Types III and IV, where considerable tissue separates the anus from the distal rectal pouch, cannot be due solely to the failure of the anal membrane to rupture. Ladd and Gross suggest that the obliterative process of the tail-gut may abnormally involve the posterior portion of the cloaca and thereby be responsible for considerable defects between the anus and the distal rectal pouch.

the present series was adequately relieved by the nurse in the admitting office when she took the routine admission temperature with a rectal thermometer.

In those patients with Types III and IV, where more tissue than a membranous diaphragm separates the anal area or pouch from the blind end of the rectum, a simple incision or direct perforation may be hazardous. In these it becomes essential to obtain a precise idea of the position of the rectal pouch. This can be determined by clinical and roentgenologic examinations. As the child cries or strains there may be no bulging of the perineum when the pouch lies high in the pelvis, but if the defect is not great, the surgeon may obtain a fairly accurate impression of the position by means of palpation alone. It is, however, unnecessary to guess about the position of the high-lying rectum for by the method of Wangenstein<sup>7</sup> an accurate localization can be made. Due to the fact that gas appears in the large intestine within twenty-four hours after birth, and will seek the distal blind rectal pouch when the child is held in the inverted position, the rectum can be clearly visualized with the x-ray by means of the fluoroscope or a roentgenogram. It may be expedient to mark the anal region with a coin or other suitable radiopaque object. (Fig. 3.)

Having determined the position of the end-gut, the surgical reconstruction is relatively simple. By making a longitudinal incision in the raphe, bleeding is held at a minimum. In view of our opinion that sphincter muscles exist in most if not all of these cases, it will readily be appreciated why we are anxious to cut through the muscle-bearing area in but one place. This can be most conveniently done by beginning the incision well anterior to the anal dimple and carrying it posteriorly into but not through the dimple and therefore the sphincteric ring. In this way we hope to cut only the anterior fibers. With the incision so placed, the problem of finding the rectum should not be great if the position has been accurately determined preoperatively by the above methods. The pouch is then freed from the surrounding tissue and brought down to the cutaneous margins where it is opened and then anchored with interrupted sutures. The perineal body is adequately restored by bringing the levator ani muscles together in front of the rectum with catgut sutures. The procedure described here is similar to that illustrated in Fig. 5 *B*. As the meconium is sterile, the danger of infection is minimal.

Following operation a tendency toward stenosis exists and, therefore, postoperative dilatation must be carried out faithfully. In some cases it has been necessary to dilate the rectum and anus first daily for weeks and later weekly for years. Fig. 4 presents a series of photographs of a patient who serves as an example of this problem. *A* was taken when the infant was 12 hours old, and before the operation had been performed. *B* was taken three days after the operation, when the infant

It is not our purpose to discuss in detail all of the surgical procedures that may be useful in dealing with these malformations. Certain general principles, however, may be useful to the experienced surgeon in adapting his individual procedure to his specific problem; further suggestions are to be found in the excellent discussions of David,<sup>4</sup> Berman,<sup>5</sup> and Chandler.<sup>6</sup>

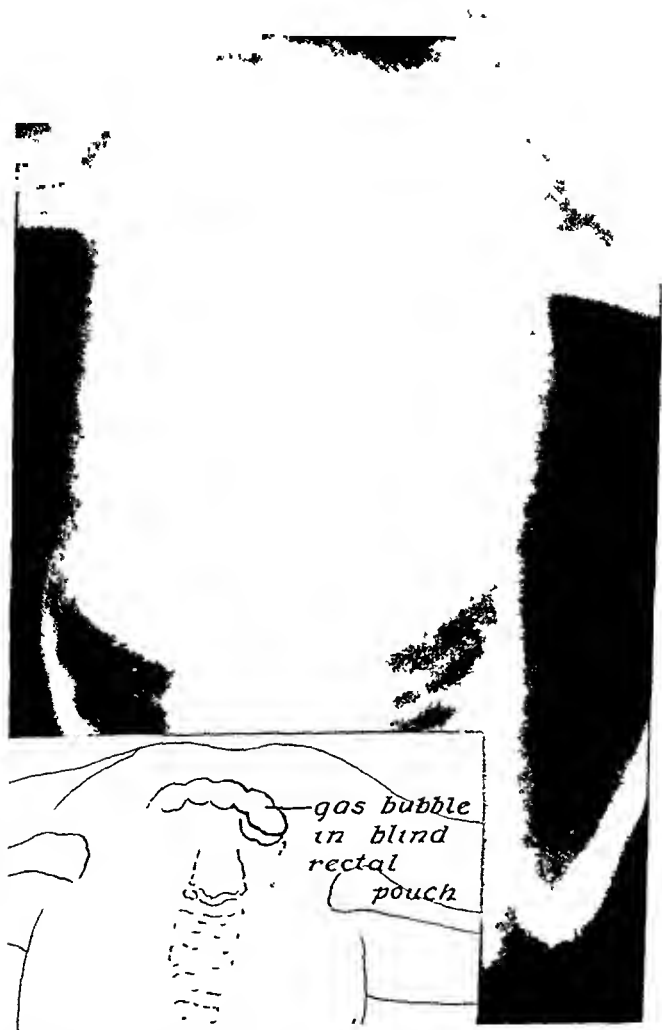


Fig 3—X-ray shadow outlining the gas-filled blind pouch of the incomplete rectum. To obtain this contrast the child is held in the inverted position.

In Types II and IV where there persists but a thin anal or rectal diaphragm, the obstructions may be adequately relieved by simple longitudinal incision or by perforation with a hemostat. The last patient in

the present series was adequately relieved by the nurse in the admitting office when she took the routine admission temperature with a rectal thermometer.

In those patients with Types III and IV, where more tissue than a membranous diaphragm separates the anal area or pouch from the blind end of the rectum, a simple incision or direct perforation may be hazardous. In these it becomes essential to obtain a precise idea of the position of the rectal pouch. This can be determined by clinical and roentgenologic examinations. As the child cries or strains there may be no bulging of the perineum when the pouch lies high in the pelvis, but if the defect is not great, the surgeon may obtain a fairly accurate impression of the position by means of palpation alone. It is, however, unnecessary to guess about the position of the high-lying rectum for by the method of Wangensteen<sup>7</sup> an accurate localization can be made. Due to the fact that gas appears in the large intestine within twenty-four hours after birth, and will seek the distal blind rectal pouch when the child is held in the inverted position, the rectum can be clearly visualized with the x-ray by means of the fluoroscope or a roentgenogram. It may be expedient to mark the anal region with a coin or other suitable radiopaque object. (Fig. 3.)

Having determined the position of the end-gut, the surgical reconstruction is relatively simple. By making a longitudinal incision in the raphe, bleeding is held at a minimum. In view of our opinion that sphincter muscles exist in most if not all of these cases, it will readily be appreciated why we are anxious to cut through the muscle-bearing area in but one place. This can be most conveniently done by beginning the incision well anterior to the anal dimple and carrying it posteriorly into but not through the dimple and therefore the sphincteric ring. In this way we hope to cut only the anterior fibers. With the incision so placed, the problem of finding the rectum should not be great if the position has been accurately determined preoperatively by the above methods. The pouch is then freed from the surrounding tissue and brought down to the cutaneous margins where it is opened and then anchored with interrupted sutures. The perineal body is adequately restored by bringing the levator ani muscles together in front of the rectum with catgut sutures. The procedure described here is similar to that illustrated in Fig. 5 B. As the meconium is sterile, the danger of infection is minimal.

Following operation a tendency toward stenosis exists and, therefore, postoperative dilatation must be carried out faithfully. In some cases it has been necessary to dilate the rectum and anus first daily for weeks and later weekly for years. Fig. 4 presents a series of photographs of a patient who serves as an example of this problem. A was taken when the infant was 12 hours old, and before the operation had been performed. B was taken three days after the operation, when the infant



was 4 days old. *C* shows the same patient four years later with a perfectly functioning anus although it is somewhat distorted by scar tissue. At the time of *C* the patient required dilatation once a month. These photographs illustrate a coexistent pseudohermaphroditism with the penis curled forward so as to resemble a clitoris. The bifid, labialike serotum contained two apparently normal testes. This situation has been recently relieved by means of reconstructive procedures.

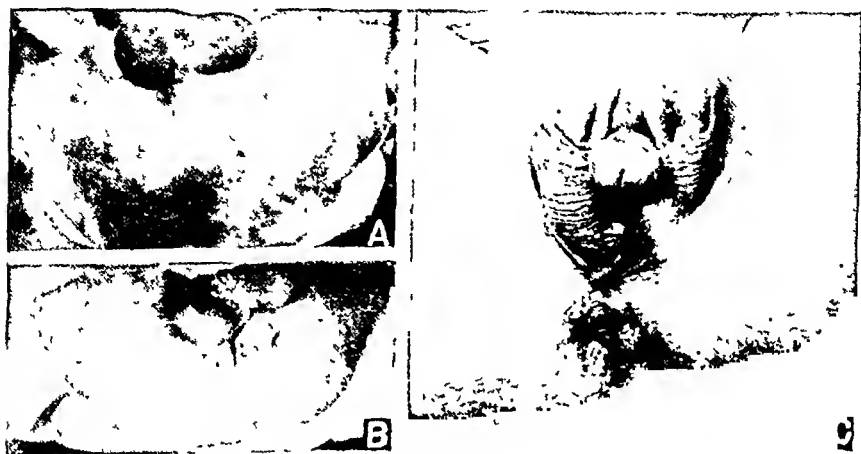


FIG. 4.—*A*. An infant 12 hours old with an anal dimple which is imperforate. *B*. Four days later, after an incision carried halfway through the dimple was made deep enough to extend into the overlying rectal pouch. *C*. The same child four years later with an open rectum and anus and a perfectly functioning anal sphincter.

The surgical supervision of these congenital anomalies varies but little in the presence of rectourethral or even rectovesical fistulas. In my own experience as has been pointed out above, the fistulas were all of the urethral variety. A case in point, with a rectourethral fistula associated with a Type III malformation, has proved particularly instructive. This patient, now 8 years old, had a colostomy performed immediately after birth, at another hospital; he was later transferred to this service. When he was 4 years old the colostomy was closed and a perineal opening was established. Postoperatively a rectourethral fistula became apparent because of a fecal urethral discharge. In addition to this complicating fistula there was a severe rectal stenosis. The severity of a stenosis generally corresponds, more or less, with the extent of the defect. In this patient the distal rectal pouch lay at the level of the pelvic inlet, so that the defect was considerable. The ordeal of frequent dilatation of the rectum, rather than the complicating fistula, was responsible for the eventual decision of the family to submit the child for further surgical treatment.

After a prolonged period of colonic irrigation the child was considered ready for operation. The urethra and rectourethral fistula were injected with an aqueous solution of methylene blue, immediately before

the operation, the catheter being left in the bladder. Prepared in this manner, the child was taken to the operating room where through a longitudinal incision in the perineum, carried posteriorly into the rectum and anus, it was possible to expose the fistulous tract in its entire extent, which was then completely excised; the urethral end being loosely closed over the indwelling catheter. The rectal opening of the tract marked the lowest point of what appeared to be normal-looking rectal mucosa, so the tract and all of the stenotic, scarred, and tortuous terminal rectum was excised. The mobilization of the suprajacent normal rectal tissue was then quite simple and the mobilized segment was easily brought down to the cutaneous margins of the anus. This procedure served to excise the fistula, cover the fistulous site, and relieve the stenosis. During this reconstructive operation no evidence of sphincter muscle was found; therefore, it seems unlikely that rectal continence will develop. Since this operation, the patient has for the first time, however, shown some control. This control appears, however, to be a matter of gluteal rather than sphincteric action, so the operation may be regarded as a therapeutic failure. From the point of view of his rectal stenosis and rectourethral fistula, however, his treatment should be regarded as quite successful.

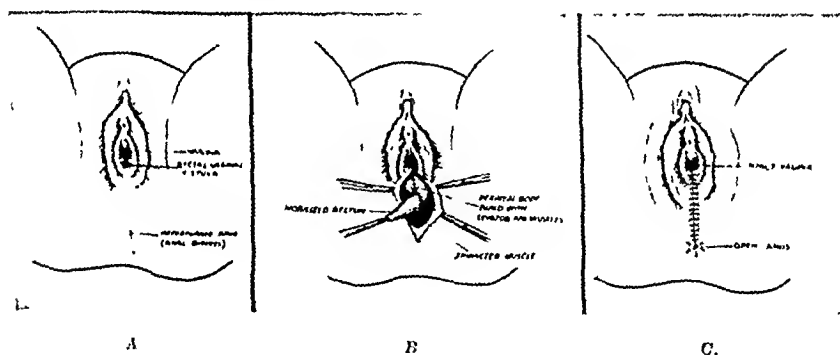


Fig. 5.—The operation used for the repair of the Type III (female) rectal anomaly associated with a rectovaginal fistula. A. The perineal view of such a fistula and the imperforate anus. B. The incision, the excision of the fistula, the mobilization of the rectum, and the reconstruction of the perineal body with the levator ani muscles. C. The completed plastic procedure: the vagina has been reconstructed, the perineum closed, and the anus has been built in the site of the imperforate dimple. The sphincter has been divided at one point to avoid destruction of the muscle.

The only fistulas seen by us in females were of the low vaginal variety. In these patients, as is often the case, the fistula was of sufficiently large caliber to permit the evacuation of feces during infancy. The operations were performed at ages of 7, 8, and 3 years, respectively. This combination of rectovaginal fistulas and the Type III anomaly is illustrated in Fig. 2.

The three sketches of Fig. 5 present our method of treating the imperforate anus of Type III in which there exists a low rectovaginal fistula. The incision is carried from the fistula posteriorly in the raphe

into, but not through, the anal dimple. The rectum and fistula are readily exposed in this way and may be completely mobilized. However, the opened free end of the fistulous tract has been found to be unsuitable for the reconstructive procedure and should be cut away. The free rectal pouch can then be brought down to the cutaneous margins of the anal dimple and anchored there with interrupted, radial sutures. This gives a complete rectovaginal septum and the perineal body can be constructed by bringing together the two levator ani muscles, with catgut sutures, in front of the rectum. In the three cases this operation has proved satisfactory from the point of view of rectal and anal patency as well as sphincteric control.

It is interesting to note that Diffenbach, of Vienna,<sup>8</sup> performed an operation similar in all essential respects to the one outlined above as early as 1826.

#### DISCUSSION

From my comments on the surgical treatment of these patients it will be noted that the importance of the perineal approach is emphasized. By means of digital and roentgenologic examinations that have been described, it is possible, I believe, to localize the blind end of the rectum with mathematical precision. The physiologic and psychologic advantages of a normally placed distal intestinal opening not only warrant but dictate heroic measures to bring about a normal anatomical relationship of the parts.

Numerous comments have been made in the past about the congenital absence of anal sphincters. As has been pointed out in the above section on embryology, the sphincter muscles arise from mesodermal components; whereas, the anus and rectum are of ectodermal and entodermal derivation. This thought alone might lead us to question the accepted order; namely, that anal and rectal defects are frequently associated with the absence of the sphincter. To be certain, it is comforting in the face of the tragedy of rectal incontinence to feel that there was a preoperative and congenital absence of sphincters. Yet careful consideration of such cases may, and often does, reveal other adequate reasons for this incontinence. In other rectal surgery we are loath to incise the sphincter muscles at more than one point lest damage to those muscles result, yet in the surgery of the absent rectum or anus such care is not stressed. It is, then, perhaps fair to ascribe some of these misfortunes to destructive surgery. In my own experience, the instances of persistent incontinence have occurred in cases where the postnatal procedure was a colostomy and in which the perineal opening was established years later. This suggests the possibility of the atrophy of disuse in the sphincter muscles.

It is difficult to support by direct testimony the belief that sphincter muscles are present in the vast majority of these cases. In a consider-

able proportion of patients the presence of a completely adequate sphincter is amply demonstrated by clinical examination and functional test; these, however, are not the cases in point. The instances that have given rise to this controversy are generally of Type III, where there is an anal dimple and a considerable underlying defect. In these patients palpation, though unsatisfactory, leads one to expect no subjacent muscle. This was precisely the clinical picture that was presented by a recent patient on our service. The infant had had a colostomy performed in another hospital because the surgeon in that institution had felt that there was no clinical evidence of an anal sphincter beneath the anal dimple. This infant died shortly after admission. Fig. 6 shows the anteroposterior and lateral x-ray views after instillation of barium solution into the colostomy. The radiopaque mixture is seen coursing through the rectourethral fistula into the urethra and up into



Fig. 6—Anteroposterior and lateral x-ray shadows demonstrating a Type III anomaly combined with a rectourethral fistula. This opaque solution was introduced through a colostomy opening and has outlined the rectal pouch, rectourethral fistula, and the urethra.

the bladder. Fig. 7 depicts the necropsy specimen taken from the same patient. The rectal pouch, fistulous tract, bladder and urethra, and the perineum have been removed intact, and then exactly hemisected. This gives a pathologic specimen which demonstrates precisely the anomaly illustrated by the male fistula diagram in Fig. 2. Careful dissection failed to demonstrate any perianal muscle tissue, but the existence of a sphincter was established by means of the microscope (Fig. 8).

Finally, it must be said in this discussion of the congenital absence of anal sphincters that our clinical impression is that most, if not all, of these patients are normally equipped with anal sphincters. Our embryological and histological evidence would seem to support this clinical observation.

The various surgical procedures have been briefly reviewed. Depending upon the type of the malformation, these patients fall into two

groups. The first group of patients requires emergency surgery because of the obstruction; those in the second group have fistulous tracts that permit the postponement of operation.

In those requiring emergency treatment because of obstruction it would seem preferable to consider the emergency as one demanding surgical intervention within the first few days, but not necessarily within the first few hours, of life. This simple concept might eliminate

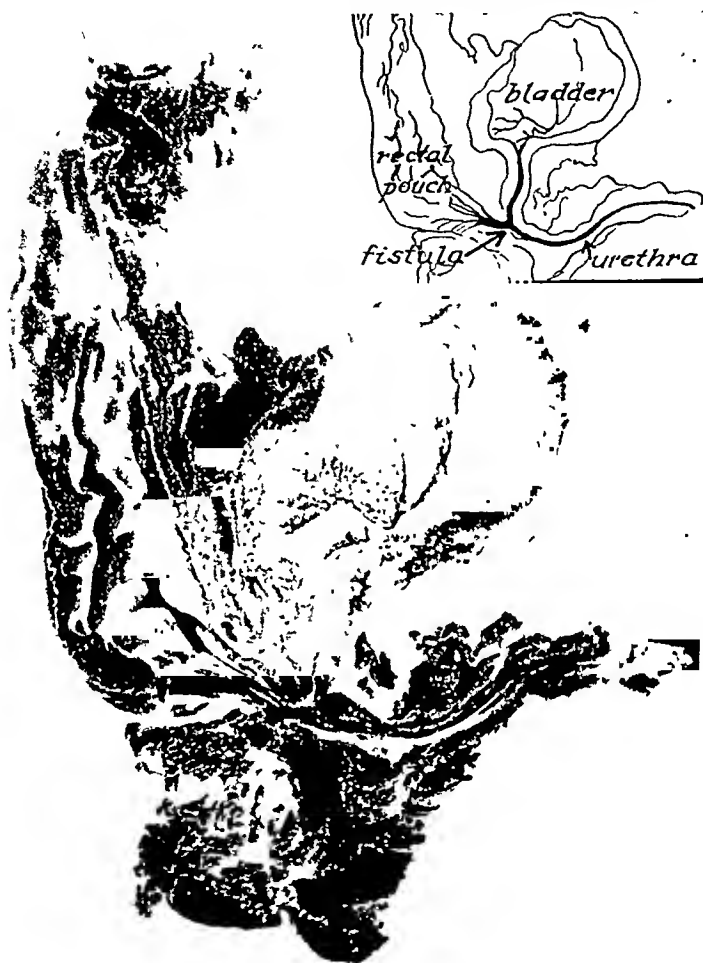


Fig. 7.—Post-mortem specimen of the patient studied in Fig. 6. The pelvic organs have been removed intact and hemisected. The bladder, urethra, rectal pouch, recto-urethral fistula, and rectal defect are demonstrated.

the casualties incident to surgical intervention in the home and it might obtain for the patients more complete examination in the hospital and more deliberate surgical consideration.

The second group, those who can have their reconstructive operations performed as elective measures, are, on the whole, a more satisfactory

group. In our series of cases this group was made up of but 3 patients; these were all of Type III in females with low rectovaginal fistulas as illustrated in Fig. 2. Many surgeons have advocated waiting for the reconstruction until these children are from 6 to 8 years old, when the structures are larger and more substantial; we have done so twice. However, in our last patient the reconstruction operation demonstrated in Fig. 5 proved eminently satisfactory at the age of 3 years. From this limited experience we are convinced that there is no real advantage in waiting more than two or three years and we also feel that the possibility of atrophy in a nonfunctioning anal sphincter may, in itself, prompt the earlier operation.

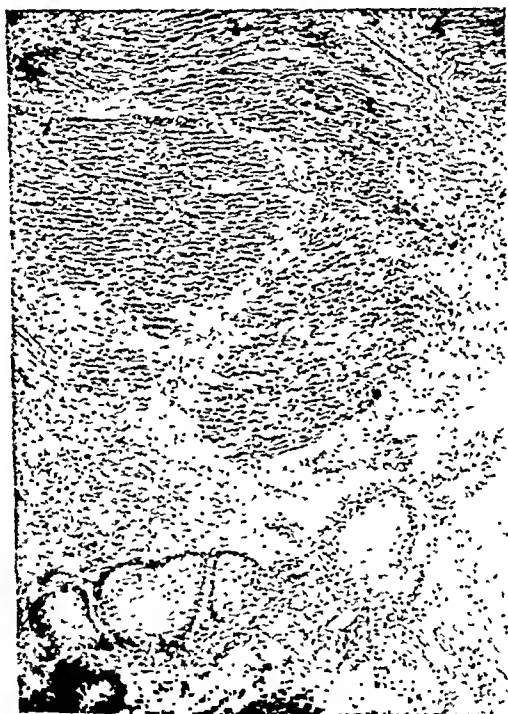


Fig. 8.—Photomicrograph demonstrating perianal muscle tissue lying immediately above subcutaneous glands. This is interpreted as sphincter muscle.

When possible, it is well to attempt the suture of the divided sphincter after anchoring the rectum in the newly formed anus. The importance of dividing the sphincter at but a single point has been stressed often in considerations of rectal surgery in general; we feel that this sound principle is no less significant in the treatment of these congenital malformations.

#### ANALYSIS OF CASES

In a series of 25 cases, 10 patients, or 40 per cent, have lived. Seven of these are regarded as having satisfactory results, due to the fact that

all fistulas are closed and that all of the patients have rectal control. Three of the results are regarded as unsatisfactory due to rectal incontinence.

Of the 15 deaths, 5 must be regarded as surgical, although 1 infant was brought to the hospital in a terminal condition following an incomplete and unsuccessful perineal operation in the home by the family physician.

The 4 other infants died in the hospital; 2 were found to have multiple congenital anomalies, 1 developed bronchopneumonia, and the fourth died of hemorrhagic disease of the newborn.

The 6 remaining patients who eventually died were all discharged from the hospital in good condition but died within five months. Two of these died from undetermined causes; 1 two weeks and the other five months after discharge. The third patient was discharged in good condition but returned a few days later and died on admission; as no necropsy was obtained the cause of death was not conclusively established. The fourth infant expired with laryngotracheal bronchitis five months after leaving the hospital. Approximately one year after discharge the fifth patient died in another hospital following the surgical correction of a rectourethral fistula. The last patient died from hemorrhage following dilatation of the rectum in the home.

#### SUMMARY

1. Twenty-five cases of malformation of the rectum and anus have been reviewed.

2. These malformations represent arrests and perversions in embryological development.

3. Of this series of patients, 21, or 84 per cent, were found in males; 4, or 16 per cent, were found in females. Seven of the males had associated rectourethral fistulas; 3 of the females had associated rectovaginal fistulas.

4. The surgical measures most useful in the treatment of these conditions have been briefly reviewed.

5. The most satisfactory therapeutic results may be expected in those patients having only a thin obstructing diaphragm and in the females with large rectovaginal fistulas that allow postponement of the operation until the patient is from 1 to 3 years old.

6. The clinical impression that most, if not all, of these patients have normal anal sphincters would seem to be supported by embryological and histological evidence.

7. Ten of the 25 patients, or 40 per cent, are still living. Seven of the 25 patients, or 28 per cent (7 of the 10 living patients, or 70 per cent), are regarded as clinical cures and have good rectal control.

8. These patients suffer a high nonsurgical mortality, partially due to the high incidence of associated congenital anomalies.

9. Physiologic and psychologic factors justify heroic measures to establish the normal anatomical relationships in malformations of the rectum and anus

The author is greatly indebted to Dr Fenwick Beekman, Director of the Children's Surgical Service of Bellevue Hospital, for his thoughtful counsel and guidance in the study of this subject and these patients. The cooperation and suggestions of Dr. Douglas Symmers, Director of Laboratories, Department of Hospitals, New York City, in the preparation of the pathologic studies and the preparation of the embryological discussion by Dr George Husser, University of California Hospital, San Francisco, Calif, are also very much appreciated

#### REFERENCES

1. Lewis, F T.. In Keibel and Mall: Manual of Human Embryology, Philadelphia, 1912, J. B Lippincott Co, vol. 2, p. 306
2. Arey, L B: Developmental Anatomy, Philadelphia, 1937, W. B. Saunders Co, p 250
- 3 Ladd, W E, and Gross, R E Congenital Malformations of the Anus and Rectum, Am J. Surg 23: 167 183, 1934.
- 4 David, V C. Embryology and Malformations of the Rectum, Lewis' Practice of Surgery, vol 7, chap 6; Nelson's Loose Leaf Living Surgery, vol. 5, pp. 161 164
- 5 Berman, J H Congenital Anomalies of the Rectum and Anus, Surg, Gynec & Obst 66: 11 22, 1938
- 6 Chandler, L R Malformations of the Anus, California & West Med 51: 84 91, 1939
7. Wangensteen, O H, and Rice, C O Imperforate Anus, A Method of Determining the Surgical Approach, Ann Surg 92. 77 81, 1930.
- 8 Dissenbach, J. F. Operative Chirurgie, Band 1: 670, 1845



# BONE TUMORS WITH REFERENCE TO THEIR TREATMENT\*

MURRAY M. COPELAND, M.D., BALTIMORE, MD.

(*From Department of Surgery, Johns Hopkins Medical School*)

IN APPRAISING any method of therapy it is necessary to know the essential pathology, the natural history of the disease, and what influence specific therapy may have upon it. The classification of bone tumors based upon the relation of bone development and subsequent tumor formation separates the tumors into specific types, each of which follows a definite course. A survey of these groups reveals more accurately the effect of treatment, and prognosis is thus placed upon a sound basis.

## CLASSIFICATION

- I. Tumors derived from precartilaginous connective tissue
  - a. Osteochondroma
  - b. Chondroma
  - c. Primary chondromyxosarcoma
  - d. Secondary chondromyxosarcoma
  - e. Osteoblastic osteogenic sarcoma
- II. Tumors related to subsequent cartilaginous growth
  - a. Bone cyst
  - b. Benign giant cell tumor
  - c. Chondroblastic sarcoma
  - d. Osteolytic osteogenic sarcoma
- III. Certain tumors of nonosseous origin intimately connected with the bone
  - a. Ewing's sarcoma
  - b. Multiple myeloma
  - c. Fibrosarcoma
  - d. Metastatic carcinoma
  - e. Angioma
  - f. Recurrent myositis ossificans
  - g. Hand-Schüller-Christian's disease

For a full description of the types of tumors, one is referred to previous publications.<sup>1-3</sup> It is the purpose of this communication to emphasize the treatment best suited for the tumor. A brief survey will be given of each group, the treatment used, and where irradiation seemed of benefit, the physical agent used. No comprehensive rule can be laid down as to whether a tumor process is radiosensitive. Experience has been our best teacher as to the behavior of tumors under radiation. A bitter lesson has been learned in that radiosensitivity does not parallel radiocurability. The term, radiosensitivity, is a relative one. A shift in the technique of giving the physical agent, either x-rays or radium, frequently reveals a change in the response of the tumor to the agent.

\*Read before the Academy of Orthopedics, New Orleans, La., Jan. 11, 1911.

Received for publication, June 3, 1911.

## I. TUMORS DERIVED FROM PRECARTILAGINOUS CONNECTIVE TISSUE

It may be said in general that tumors of this group are not radio-sensitive, while isolated examples may be pointed out in which the growth of the tumor has been affected by irradiation, or where the x-rays and gamma rays have been used successfully as an adjunct to surgery.

*Osteoma or osteochondroma* is primarily a surgical problem when treatment is necessary. This is the largest group of benign tumors arising from precartilaginous connective tissue in the skeleton.<sup>4 6</sup>

These neoplasms are most frequent near the ends of the long bones of patients between the ages of 10 and 25 years. The distinctive diagnostic features are the pedicle of normal bone protruding from the bone cortex and the rim of cartilage overlaying it. A similar structure may be seen microscopically. In the x-ray picture is depicted the compact differentiated outgrowth of bone and an overlaying cartilaginous cap flecked with calcium. Cases of single osteochondromas without symptoms frequently go unnoticed. They may be left untreated but should be watched by interval x-ray examinations, since they may undergo secondary malignant change, particularly after the age of 30 years. Histogenetically, an exostosis represents a failure in the accurate approximation of tendon and cortex, with proliferation of cartilage from the tendon and protrusion of proliferating cortex. Simple excision usually suffices to cure those osteochondromas which produce pain or dysfunction.

In the hereditary or multiple exostoses<sup>1 7 8</sup> treatment is more difficult. The regions most frequently and severely affected are those of the forearm and foreleg, the bones of which may be fused at one point. The prognosis as far as life is concerned is good, but there is no adequate form of treatment except operation for correction of deformities as in single osteochondroma. In a few cases with multiple skeletal involvement, I have observed secondary malignant change in the cartilaginous growths resulting in death from chondromyxosarcoma. X-ray or radium therapy plays little role in the treatment of these cases.

*Chondroma* is a common type of cartilaginous tumor often classified with the benign exostoses.<sup>1 1</sup> It occurs in the small bones of the hands and feet, also in the spine, ribs, and sternum. In the small pipe bones it appears as a central lesion with rarefaction, visible in the roentgenogram as a cystic area, within a shell of cortical bone. It is rarely multiple and rarely affects long bones. In deciding whether a particular chondroma is to be treated from the benign or malignant standpoint, the location and not the pathologic changes must be given primary consideration. Chondromas in the small bones of the hands and feet are to be looked upon as benign lesions curable by thorough extirpation (cutting and cauterization). True chondromas of large size occurring about the sternum or spine or in the long bones must be looked upon as potentially malignant. They should be removed if possible. X-ray

# BONE TUMORS WITH REFERENCE TO THEIR TREATMENT\*

MURRAY M. COPELAND, M.D., BALTIMORE, MD.

(From Department of Surgery, Johns Hopkins Medical School)

IN APPRAISING any method of therapy it is necessary to know the essential pathology, the natural history of the disease, and what influence specific therapy may have upon it. The classification of bone tumors based upon the relation of bone development and subsequent tumor formation separates the tumors into specific types, each of which follows a definite course. A survey of these groups reveals more accurately the effect of treatment, and prognosis is thus placed upon a sound basis.

## CLASSIFICATION

- I. Tumors derived from precartilaginous connective tissue
  - a. Osteochondroma
  - b. Chondroma
  - c. Primary chondromyxosarcoma
  - d. Secondary chondromyxosarcoma
  - e. Osteoblastic osteogenic sarcoma
- II. Tumors related to subsequent cartilaginous growth
  - a. Bone cyst
  - b. Benign giant cell tumor
  - c. Chondroblastic sarcoma
  - d. Osteolytic osteogenic sarcoma
- III. Certain tumors of nonosseous origin intimately connected with the bone
  - a. Ewing's sarcoma
  - b. Multiple myeloma
  - c. Fibrosarcoma
  - d. Metastatic carcinoma
  - e. Angioma
  - f. Recurrent myositis ossificans
  - g. Hand-Schüller-Christian's disease

For a full description of the types of tumors, one is referred to previous publications.<sup>1-3</sup> It is the purpose of this communication to emphasize the treatment best suited for the tumor. A brief survey will be given of each group, the treatment used, and where irradiation seemed of benefit, the physical agent used. No comprehensive rule can be laid down as to whether a tumor process is radiosensitive. Experience has been our best teacher as to the behavior of tumors under radiation. A bitter lesson has been learned in that radiosensitivity does not parallel radiocurability. The term, radiosensitivity, is a relative one. A shift in the technique of giving the physical agent, either x-rays or radium, frequently reveals a change in the response of the tumor to the agent.

\*Read before the Academy of Orthopedics, New Orleans, La., Jan. 11, 1941.  
Received for publication, June 3, 1941.

change appears as a fuzzy infiltrating periosteal shadow flecked with calcium. Destruction of the cortical bone follows, occasionally with pathologic fracture.

Microscopically, the tumor is composed of cartilage, large amounts of myxomatous tissue, calcified cartilage, and proliferating connective tissue elements. The age of onset is much later than in primary chondrosarcoma, usually over the age of 25 years. The upper humerus, ribs, and heel are frequent sites of origin. Of 18 cases (26 per cent) surviving five years or more up to 1935, 6 patients received irradiation: 2 in combination with curettement only and 4 with resection only. In 4 cases with resection and no irradiation the patients have survived five years or longer. Eight cases had primary amputation. It would seem, therefore, that while irradiation may be of benefit as an adjunct to surgery, the relative benignity of the lesion plays a more important role in the cure of the tumor process.

*Osteoblastic Osteogenic Sarcoma.*—This is the most highly differentiated type of osteogenic sarcoma.<sup>1, 2, 12, 13</sup> Fibrous elements may predominate microscopically, but usually proliferation of osteoblasts and new bone formation are seen, with rare islands of cartilage. This tumor is most frequent between the ages of 15 and 25 years and is usually situated in either the lower end of the femur or the upper end of the tibia. Other locations are the upper humerus, ribs, vertebrae, and pelvis.

The x-ray picture is characterized by dense, radiating, new bone in the periosteal zone, giving a "sun-ray" appearance. Later the medullary cavity is obliterated by tumor bone with some secondary destruction of the cortex. Histologically, the tumor is composed of large osteoblasts with a conglomerate scattering of osteoid substance (Fig. 2). Cures have been achieved in 26 per cent of the cases. Of 18 patients surviving five years, 5 received irradiation as an adjunct to surgery (largely amputation). In 1 individual, with a lesion in the lower femur, following exploration and chiseling away of the tumor, the area was exposed to the radium pack. Later the leg was amputated. This patient survived twelve years after the amputation. This result again may be attributed to cell differentiation with some natural restraint factor present.

From this study it becomes increasingly clear that the cell differentiation of the tumor process plays an important role in the prognosis and in addition, that radical extirpation is the procedure of choice.

## II. TUMORS RELATED TO SUBSEQUENT CARTILAGINOUS GROWTH

*Bone Cyst.*<sup>1, 14, 28</sup>—The benign solitary bone cyst is frequent in children under the age of 18 years. It usually occurs in the shaft near the upper ends of the humerus, femur, or tibia and runs a protracted and benign course. Pathologic fracture is the only acute phase of the disease

or telerradium therapy has been of benefit in retarding the growth in four cases. One patient survived eighteen years after diagnosis, with repeated series of x-ray treatments.

*Primary chondromyxosarcoma* is a form of periosteal osteogenic sarcoma.<sup>1, 10</sup> It arises primarily in young patients (aged 14 to 21 years) and at the sites where tendons insert directly into the bone. The favorite sites are about the knee, in the lower femur or upper tibia, also at the shoulder and pelvic girdles. The neoplasm is composed of tumor cartilage, some ossification, and areas of cystic destruction (Fig. 1, A and B). In the x-ray it appears as a subperiosteal shadow streaked with calcium spicules. It does not involve the cortex until late in the disease, causing bone destruction. Permanent cures in this group average 9 per cent. Three of five cases surviving five years or more re-



Fig. 1.—Photomicrographs of primary chondromyxosarcoma. A, embryonic connective tissue with the fetal cartilage cells; B, fully developed myxomatous tissue. This tumor is highly radioresistant.

showing A, proliferation of matrix containing many cells with areas of fetal

ceived irradiation in conjunction with amputation. All surviving patients had amputation performed, suggesting irradiation had little or no influence on the results. Irradiation, however, relieved pain in many instances and reduced soft part swelling.

*Secondary chondrosarcoma* is a malignant tumor arising on the basis of a pre-existing chondroma or osteochondroma, occasionally complicating Paget's disease or hereditary chondrodysplasia.<sup>1, 11, 12</sup> Most of the patients are between the ages of 35 and 55 years. The locations of the tumor show a tendency for the regions about the upper humerus, ribs, femur, and heel to be involved.

In the x-ray picture it is most easily diagnosed where a portion of the primary lesion still remains and where the superimposed malignant

change appears as a fuzzy infiltrating periosteal shadow flecked with calcium. Destruction of the cortical bone follows, occasionally with pathologic fracture.

Microscopically, the tumor is composed of cartilage, large amounts of myxomatous tissue, calcified cartilage, and proliferating connective tissue elements. The age of onset is much later than in primary chondrosarcoma, usually over the age of 25 years. The upper humerus, ribs, and heel are frequent sites of origin. Of 18 cases (26 per cent) surviving five years or more up to 1935, 6 patients received irradiation: 2 in combination with curettement only and 4 with resection only. In 4 cases with resection and no irradiation the patients have survived five years or longer. Eight cases had primary amputation. It would seem, therefore, that while irradiation may be of benefit as an adjunct to surgery, the relative benignity of the lesion plays a more important role in the cure of the tumor process.

*Osteoblastic Osteogenic Sarcoma.*—This is the most highly differentiated type of osteogenic sarcoma.<sup>1, 2, 12, 13</sup> Fibrous elements may predominate microscopically, but usually proliferation of osteoblasts and new bone formation are seen, with rare islands of cartilage. This tumor is most frequent between the ages of 15 and 25 years and is usually situated in either the lower end of the femur or the upper end of the tibia. Other locations are the upper humerus, ribs, vertebrae, and pelvis.

The x-ray picture is characterized by dense, radiating, new bone in the periosteal zone, giving a "sun-ray" appearance. Later the medullary cavity is obliterated by tumor bone with some secondary destruction of the cortex. Histologically, the tumor is composed of large osteoblasts with a conglomerate scattering of osteoid substance (Fig. 2). Cures have been achieved in 26 per cent of the cases. Of 18 patients surviving five years, 5 received irradiation as an adjunct to surgery (largely amputation). In 1 individual, with a lesion in the lower femur, following exploration and chiseling away of the tumor, the area was exposed to the radium pack. Later the leg was amputated. This patient survived twelve years after the amputation. This result again may be attributed to cell differentiation with some natural restraint factor present.

From this study it becomes increasingly clear that the cell differentiation of the tumor process plays an important role in the prognosis and in addition, that radical extirpation is the procedure of choice.

## II. TUMORS RELATED TO SUBSEQUENT CARTILAGINOUS GROWTH

*Bone Cyst.*<sup>1, 14, 24</sup>—The benign solitary bone cyst is frequent in children under the age of 18 years. It usually occurs in the shaft near the upper ends of the humerus, femur, or tibia and runs a protracted and benign course. Pathologic fracture is the only acute phase of the disease

and probably the most frequent reason for consulting a physician. The x-ray picture shows a central expanded bone defect, symmetrical and regular in contour.

Microscopically, a healing bone reaction is noted about the cavity which may be lined by fibrous tissue. It usually is filled with straw-colored fluid or remains of old hemorrhage. Some cysts are trabeculated.

Spontaneous arrest of the lesion without obliteration of the cavity results in the latent bone cyst. Fracture through the cyst usually results in healing.

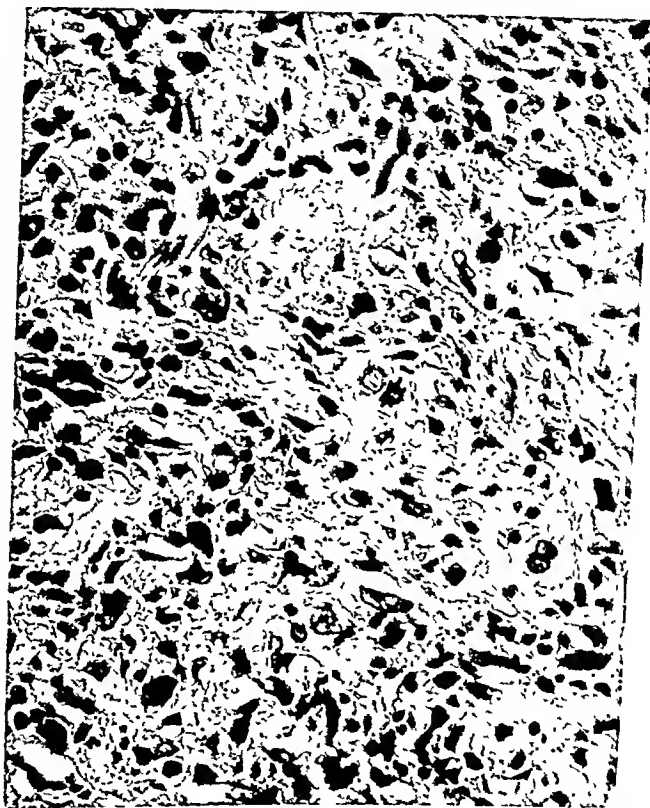


Fig. 2.—Photomicrograph showing large tumor osteoblasts and the osteoid intercellular substance typical of sclerosing osteogenic sarcoma. This tumor is radioresistant.

Variations of the simple bone cyst may be encountered:

1. *Giant-cell variant* of the bone cyst<sup>1, 15</sup> in which the duration of symptoms is found to be shorter; located invariably near the epiphysis of the bone on the metaphyseal side. It is most commonly found in the greater trochanter of the femur and lower radius. In the x-ray it is polycystic in character, more subcortical than central, and most frequently trabeculated.

Microscopically, the walls are lined by fibrous stroma containing variable numbers of giant cells. Hemorrhage is common. These lesions stand midway between the typical bone cyst and giant-cell tumor.

2. *Polycystic osteitis fibrosa*,<sup>1, 2</sup> a multilocular structure occurring either as a single lesion or with generalized osteitis fibrosa cystica. The cysts also occur near the epiphysis on the metaphyseal side, but extend over a considerable area of the bone shaft. The duration of symptoms averages about five months. In the x-ray they appear as an aggregation of small cysts, which have more or less coalesced, giving a polycystic appearance with some expansion of the cortex.

Histologically, there are many small cysts, usually filled with blood and surrounded by giant cells. Varying amounts of fibrous tissue may be seen.

3. *Multiple osteitis fibrosa cystica*, a generalized demineralization of bones due to hyperparathyroidism.<sup>1, 16, 17</sup> Rarefaction of bone, bending deformities, cystic tumor areas, and fractures are noted. Bone involvement is most pronounced in the pelvis, spine, and long bones. The microscopic picture may show typical giant-cell tumor or healing bone reaction, depending on the activity of the disease.

The prognosis as to life is good in all forms of bone cysts and osteitis fibrosa.

In the solitary bone cyst of the adult in which symptoms are absent, no treatment is indicated.

In the solitary bone cyst of young people, where fracture has occurred and the position of the fragments is satisfactory, simple fixation gives a good result.

If the lesion is progressive after several months, exploration and curettement, followed by chemical cauterization, is indicated. Bone chips or crushing of the bone shell may be used to obliterate the cavity.

In the acute bone cyst (giant-cell variant) moderate amounts of x-ray therapy given in divided doses<sup>29</sup> is considered adequate treatment. Should irradiation fail, operative interference may be necessary. Primary curettement and cauterization yield excellent results. Irradiation followed by surgical procedures gives less satisfactory healing in the aggressive bone cysts.

In multiple osteitis fibrosa the possibility of parathyroid tumor must be ruled out, and if suspected, the region of the glands should be explored surgically or irradiated.<sup>18, 19</sup> A diet rich in calcium, phosphorus, and vitamin D is a necessary adjunct to the therapy.

*Benign Giant-Cell Tumor*.<sup>1, 20</sup>—An epiphyseal lesion occurring after the age of 18 years. It is most frequent in the lower end of the femur, upper end of the tibia, and lower end of the radius.

The duration of symptoms averages fourteen months. The sequence of events is trauma, pain, tumor, and occasionally pathologic fracture. In the x-rays an early giant-cell tumor shows a defect situated asymmetrically in an epiphysis. The defect is surrounded by a bone shell which may be perforated. The lesion is progressive and in a few instances may show sarcomatous degeneration.

Microscopically, the tumor is composed of large multinucleated giant cells embedded in a mass of small round cells. The giant cells average



over 30 per low-power field and the number of nuclei per cell varies from 15 to 200. The giant cells are more numerous about hemorrhage, spicules of old bone, or small cystic areas (Fig. 3). There are a number of variants of giant-cell tumor. Certain lesions of sesamoid bones and in the jaw about the teeth are related pathologically to giant-cell tumor.

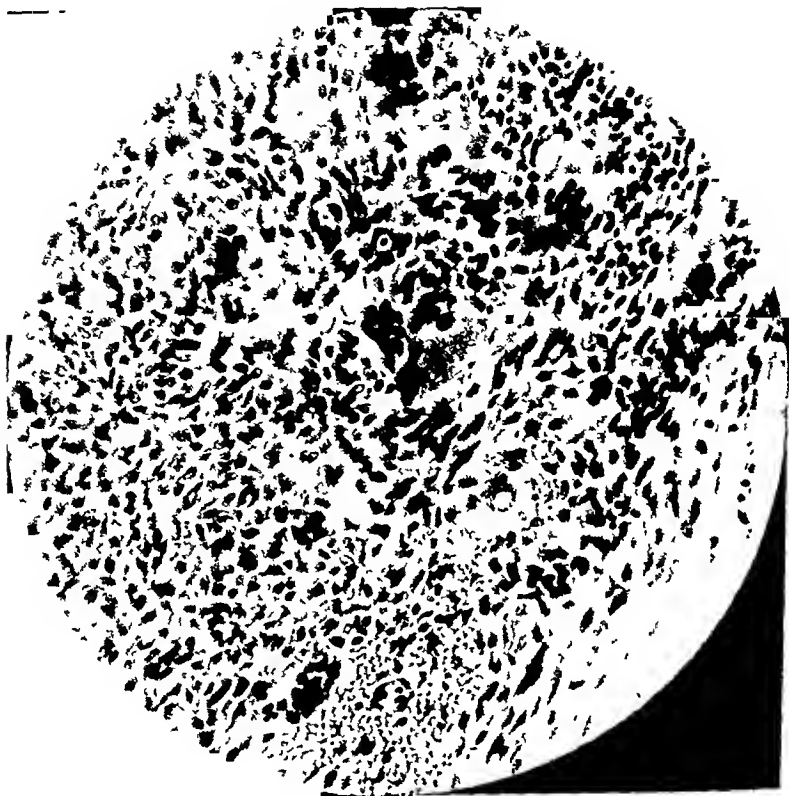


Fig. 3.—Photomicrograph of giant-cell tumor. Giant cells are embedded in a stroma of small round cells and spindle cells. Many small blood vessels are present. Damage to these capillaries represents a factor in the radiosensitivity of this tumor.

Perhaps 85 per cent of giant-cell tumors can be accurately diagnosed on the history, physical examination, and roentgenographic studies. There is increasing evidence, however, that a definite percentage will show malignant degeneration.<sup>21, 22, 23</sup> Because of this fact, any doubtful or atypical case must be biopsied, followed by thorough curettage and cauterization if benign, or by such radical procedure as may be indicated if malignant.

Conservatism in the treatment of giant-cell tumor has been increasing since 1912.<sup>23, 24</sup> If one has to consider the economy of time, surgery is the procedure of choice.<sup>26, 27</sup> In a primary case, not too advanced, curettage followed by cauterization is advocated, especially in the lower femur and the upper tibia. In advanced lesions of the ulna, fibula,

or radius, resection or irradiation may be used. Recurrences may be troublesome and call for further curettement or even resection where possible. They are usually due to incomplete removal, perforation of the bone shell, or declining reaction of the cortex due to age.

Many giant-cell tumors are radiosensitive, but the mechanism of response is not well understood.<sup>30</sup> Opinion varies greatly on the efficacy of irradiation versus surgical intervention in benign giant-cell tumor. It is well established that certain lesions irradiated alone or treated by surgery alone heal perfectly, but the combination of the two is not advocated. Many unfortunate results have accrued from such combination of therapy.

Results by irradiation are less favorable in the weight-bearing bones.<sup>31</sup> Suberythema doses of irradiation, given with sufficient intervals of time, are an important factor in avoiding deformity and other complications.

There are many giant-cell tumors which are inoperable because of their location or extent of the disease and in which x-ray therapy will adequately control the process.

Irradiation should be given sparingly near an epiphysis of a growing bone.

Pre- and postoperative x-ray therapy have little place in the treatment of giant-cell tumor.

*Chondroblastic Sarcoma.*—This is a rare osteolytic variant of osteogenic sarcoma, sometimes erroneously called cartilaginous giant-cell tumor.<sup>1, 32</sup> It arises from a proliferation of cartilage, at the epiphyseal line, during the age of puberty. It may be seen about the upper end of tibia, lower end of femur, and upper end of humerus. The duration of symptoms prior to operation averages five months.

In the x-ray picture there is a characteristic mottled cystic area of bone destruction, with expansion of the bone shell and usually some periosteal reaction. Not infrequently the tumor bears a marked similarity to giant-cell tumor.

Microscopically, one sees masses of young and adult cartilage undergoing calcification, with areas of uncalcified matrix. The tumor is extremely vascular. Near the vascular areas and about the periphery of the cartilage numerous giant-cell osteoblasts are seen (Fig. 4). Many of these tumors are quite malignant, but irradiation has been a most effective method of treatment in many of the patients who have survived. In fact, in the majority of cases the cures which are recorded are largely due to x-ray and radium therapy. The lesion is not particularly radiosensitive and requires large amounts of irradiation to control it. Three of 6 five-year survivals are attributed to the use of x-ray and radium without curettement. An amputation alone proved successful in 1 case. It, therefore, seems logical to recommend radium

or x-ray therapy (Coutard method) following exploration, unless the tumor occurs in a bone which can be resected without sacrifice of function.

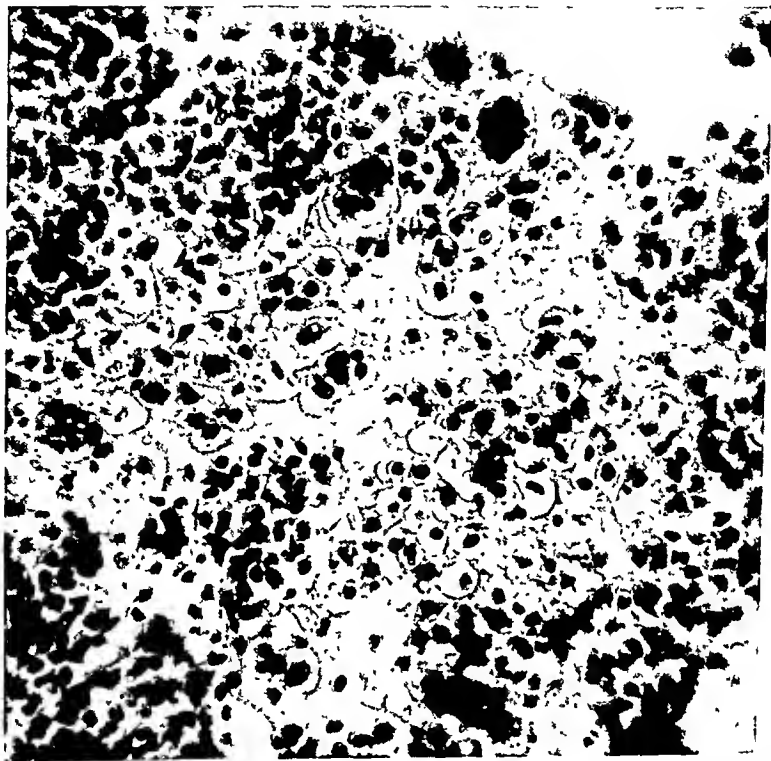


Fig. 4.—Photomicrograph of chondroblastic sarcoma. Note the proliferation of chondroblasts with small amounts of calcified cartilage. Giant-cell invasion about the area of calcification is taking place. While not radiosensitive, the majority of five-year survivals in this tumor have been effected by intensive irradiation.

*Osteolytic Osteogenic Sarcoma.*—This is a destructive tumor arising in the region of the marrow cavity in the shaft of the long bones.<sup>1, 2</sup> It seems to be related to the formation of cancellous bone which normally follows in the wake of calcified cartilage.

Clinically, the tumor is usually observed about one year after the beginning of symptoms. It has a wide age distribution, being most frequent in young adults. The tumor has an unusual tendency to involve the shaft and to produce a pathologic fracture.

The roentgenograms may be hard to interpret and are often confused with benign bone cyst, giant-cell tumor, metastatic carcinoma, and Ewing's sarcoma.

The distinguishing features in the x-ray film are the melting away and perforation of the bone shell at an early stage when the lesion is asymmetrically located, the presence of a periosteal reaction, and the slight degree of cortical expansion. In advanced cases osseous destruction leaves little doubt of malignant change in the bone.

Microscopically, large spindle cells and large abortive osteoblasts with numerous mitotic figures and small amounts of osteoid tissue are seen (Fig. 5).

*Radiosensitivity:* The tumor is not sensitive to x-ray or radium and does not respond to therapeutic doses.

Amputation only has been effective in giving 7 (10 per cent) five-year survivals.

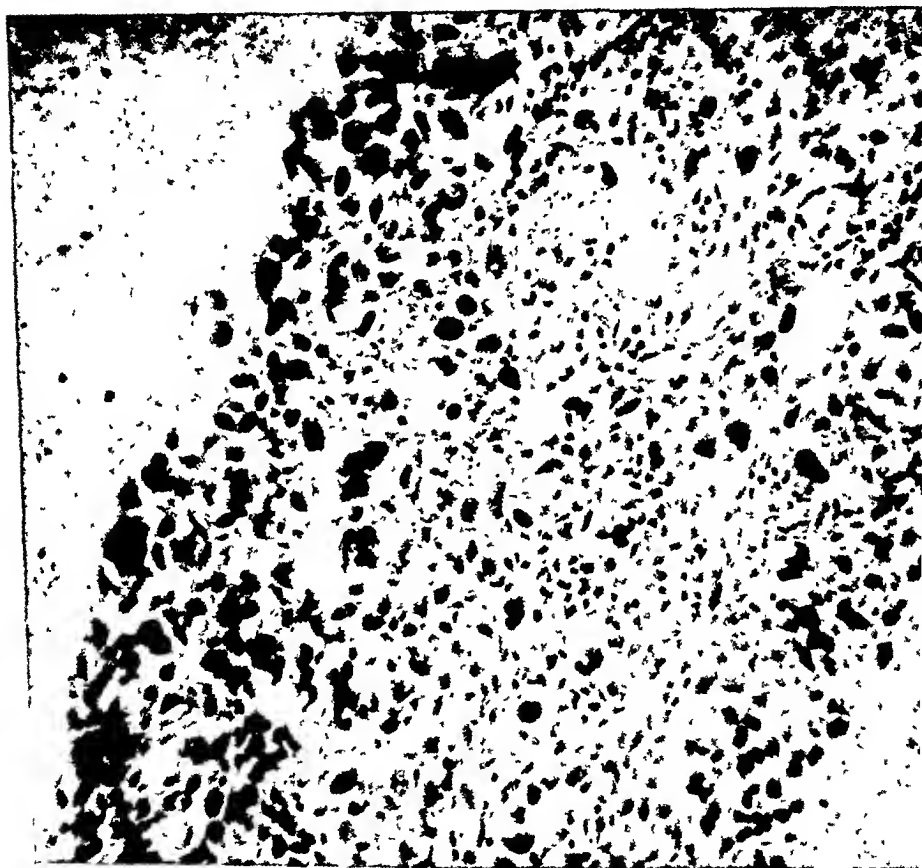


Fig. 5.—Photomicrograph showing abortive osteoblasts, hyperchromatism, and pleomorphism typical of osteolytic osteogenic sarcoma. Large vascular areas are frequently found in this tumor. It is quite radioresistant.

### III. CERTAIN TUMORS OF NON-OSSEOUS ORIGIN INTIMATELY CONNECTED WITH THE BONE

1 *Ewing's Sarcoma*.—This malignant tumor which arises intra-cortically or subperiosteally occurs in the first two decades of life; it involves the metaphysis primarily, most often affecting the long pipe bones, especially the tibia and femur<sup>2, 7, 11</sup>. The disease never involves the epiphysis primarily. It shows the usual symptoms of pain and tumor followed by dysfunction.

or x-ray therapy (Coutard method) following exploration, unless the tumor occurs in a bone which can be resected without sacrifice of function.

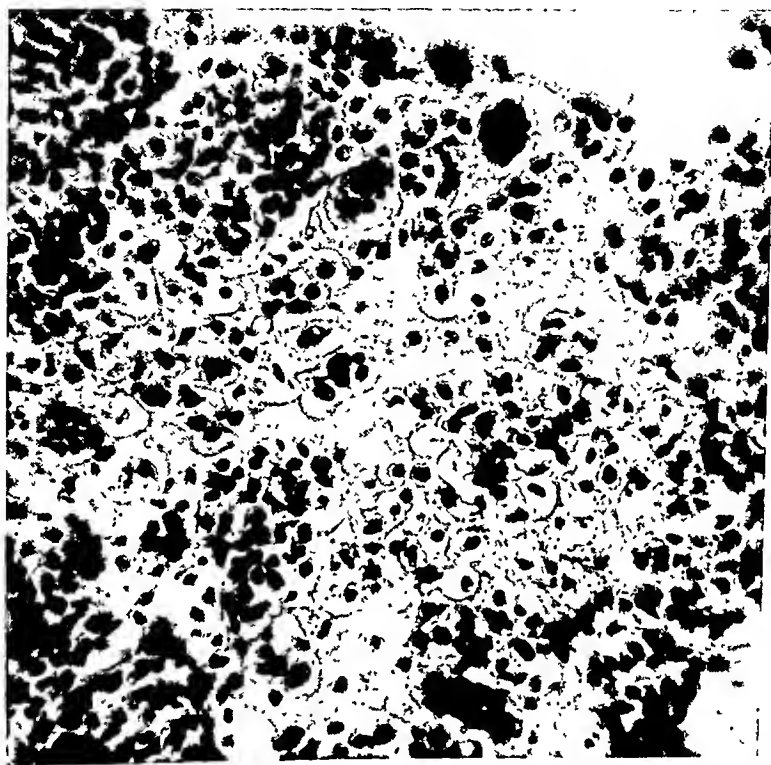


Fig. 4.—Photomicrograph of chondroblastic sarcoma. Note the proliferation of chondroblasts with small amounts of calcified cartilage. Giant-cell invasion about the area of calcification is taking place. While not radiosensitive, the majority of five-year survivals in this tumor have been effected by intensive irradiation.

*Osteolytic Osteogenic Sarcoma.*—This is a destructive tumor arising in the region of the marrow cavity in the shaft of the long bones.<sup>1, 2</sup> It seems to be related to the formation of cancellous bone which normally follows in the wake of calcified cartilage.

Clinically, the tumor is usually observed about one year after the beginning of symptoms. It has a wide age distribution, being most frequent in young adults. The tumor has an unusual tendency to involve the shaft and to produce a pathologic fracture.

The roentgenograms may be hard to interpret and are often confused with benign bone cyst, giant-cell tumor, metastatic carcinoma, and Ewing's sarcoma.

The distinguishing features in the x-ray film are the melting away and perforation of the bone shell at an early stage when the lesion is asymmetrically located, the presence of a periosteal reaction, and the slight degree of cortical expansion. In advanced cases osseous destruction leaves little doubt of malignant change in the bone.

In the x-ray picture the lesions show as multiple punched-out areas varying from 1 to 5 cm. or more in diameter. In the skull the area of rarefaction appears between the inner and outer tables of bone.

Microscopically, the tumor is composed of plasmalike cells, with eccentric nuclei containing spokelike arrangement of the chromatin. Fusiform cells and binucleate giant cells are also present (Fig. 7).

The lesion is moderately radiosensitive and among the palliative measures x-ray or radium therapy is outstanding. Control of pain, recalcification of pathologic fracture and areas of bone erosion have been accomplished under this treatment. Symptomatic improvement is the rule and life may be prolonged from two to four years.

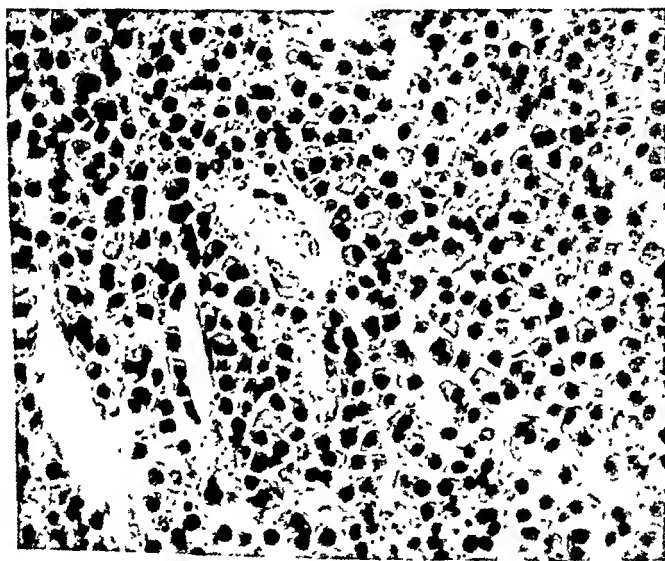


Fig. 7.—Typical plasma cell type of multiple myeloma. This tumor is moderately radiosensitive.

3. *Fibrosarcoma* may be of periosteal (fascial sheath) or neurogenic origin.<sup>1, 2, 70</sup> It may extend in two directions both outside and beneath the periosteum. This form of sarcoma represents only about 1.5 per cent of all neoplasms of bones. The majority of periosteal fibrosarcomas are of a low degree of malignancy. The age of the patient is usually well over 30 years. In only 2 cases of neurogenic sarcoma studied by us was the lesion found in a child. The average duration of symptoms is about one year. It most frequently involves the femur and tibia, but other bones may be affected.

In the x-ray picture there is usually a large soft-part shadow. The bone shows erosion from without. The reaction of the bone is variable. The periosteum may show varying degrees of distorted ossification or no response at all. Bone destruction may be extensive. The ratio of soft-part tumor to bone destruction is important.

In the roentgenogram a widening of the shaft, with increase in cortical structure and onion-peel periosteal reaction, is an early finding followed later by varying degrees of bone destruction.

Microscopically, the tumor is composed of small round cells, with dense nuclei and scanty cytoplasm simulating a lymphosarcoma (Fig. 6).

Irradiation provides a good therapeutic test and the best available palliative therapy. Irradiation alone, however, is not sufficient to control the disease in the majority of cases.

A review of our patients,<sup>1, 34</sup> the Bone Sarcoma Registry<sup>35</sup> cases, and the cases of Coley<sup>36</sup> leads to the conclusion that combined preoperative irradiation (Coutard method) in full therapeutic dosage, followed by amputation or radical resection, gives the best results (9 per cent five-year survivals).

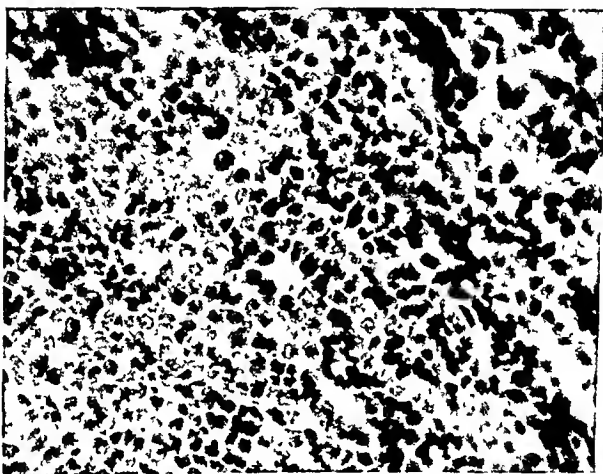


FIG. 6.—Photomicrograph showing the characteristic cells of Ewing's sarcoma. Note the indistinct cytoplasm and the round and oval nuclei. This tumor is quite radio-sensitive.

Irradiation alone has been responsible for five-year survivals in 2 of our cases: one a patient in whom the tibia was explored, curetted, and then given intensive x-ray treatment. Another patient clinically showed Ewing's sarcoma in the femur, refused operation, received intensive x-ray treatment. This leg was amputated six years later because of the radiation fibrosis. No residual tumor was found. Resection of the clavicle and a portion of the scapula in successive cases, followed by intensive x-ray therapy, has yielded five-year survivals.

2. *Multiple Myeloma*.—This is a rare form of tumor developing in multiple foci in the red bone marrow of adults.<sup>1, 37, 38</sup> The ribs, spine, pelvis, femur and skull are most frequently affected. The patients are usually in the sixth decade of life. Pathologic fracture occurs in 62 per cent of the cases. Bence-Jones bodies appear in the urine in about 65 per cent of the cases. Remissions of the disease are spontaneous.

neural tumors from the benign neurofibromas to the most malignant form of neurogenic sarcoma. The more malignant and cellular forms predominate the picture where bones are involved.

Neurogenic sarcomas as a group are highly radioresistant tumors. Interstitial irradiation by buried radon implants has been almost uniformly disappointing. A certain number of cases has shown some regression by external irradiation alone.

It may be stated, however, that clinical cures in neurogenic sarcoma, are obtained only by surgical intervention. The best results are obtained by early amputation, and even with this radical form of treatment, permanent cures are not numerous.

4. *Metastatic carcinoma* of bone is usually seen in late adult life.<sup>1, 2, 39-41</sup> It affects the bones in an extremely variable manner. About one-half of the lesions may occur as a single focus in the ends of the long bones, producing a central area of bone destruction, while the other half may involve the skeleton diffusely, producing either osteolytic or osteoplastic changes. The source of the tumor varies, but the most frequent sites of the primary growth are: cancer of the breast, hypernephroma, cancer of the prostate, thyroid, and somewhere in the female genitals or gastrointestinal tract. Solitary areas of metastatic carcinoma to bone occur most frequently in the spine and in the upper end of the humerus or femur, and are extremely rare below the knee or elbow. They may also involve the trunk or the skull. A central area of bone destruction as seen in the x-ray, rapidly increases and destroys the cortex from within, outwardly with little bone expansion. Multiple areas of skeletal involvement by metastatic tumors may also be osteolytic in character and central in location. Such lesions have a tendency to involve the pelvis and the spine in addition to the upper ends of the humerus and femur. Pathologic fracture is common. In the roentgenogram they are visible as confluent and mottled areas of bone destruction in medullary locations. Osteoplastic involvement of the bones by skeletal metastases is most frequently a diffuse affair, and in addition to the absorption of bone always present, there is a laying down of irregular new bone of moderate density.

The outcome of these cases is uniformly fatal, but palliation and prolongation of life may be achieved by irradiation with x-rays or radium, and some of these patients may live for a period as long as five years.

No rule can be laid down as to treatment. The general condition of the patient must be considered, and a careful balance must be maintained between the amount of irradiation given and the benefit rendered.

5. *Angioma of bone* is considered rare.<sup>42, 43</sup> We have observed only 12 cases. The ages of the patients vary between 4 and 40 years. The tumors are located in the humerus (4 cases), ulna, radius, femur, os calcis, skull, and vertebrae.



Microscopically, the spindle cell varies from the more aggressive oat-cell type to the large fusiform spindle cell, with transition cell forms (Fig. 8). There is usually no bone or cartilage seen in the fibrosarcomas. A definite percentage of the fascial sheath tumors are not sarcomas but cellular fibromas. This accounts in part for the unusual number of cures of so-called fibrosarcoma.

These tumors are not highly radiosensitive. The cell differentiation is all important in this group. There is some evidence that irradiation inhibits tumor growth for a time, producing a slow sclerosing reaction in the fibrospindle-cell type of lesion. Cases with the fibrospindle-cell variety of tumor will survive five years or longer, no matter the inadequacy of the treatment. Amputation or radical resection cures the majority of patients.

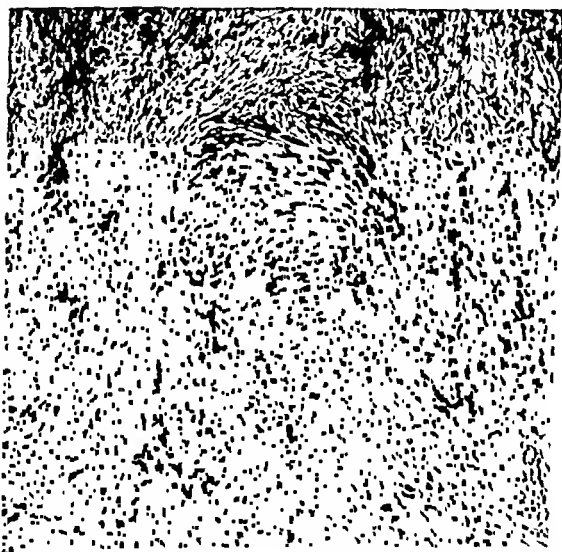


Fig. 8.—Low-power micrograph of the fibrospindle-cell sarcoma. The prognosis in this grade of tumor following a radical operation is extremely favorable. This tumor.

The undifferentiated oat-cell type of fibrosarcoma is extremely aggressive and neither x-ray treatment, radium, nor local excision offers a permanent cure. Primary amputation where possible is the treatment of choice.

The neurogenic sarcomas, invading bone, are differentiated microscopically by the myxomatous structure intermingled with the fibrous tissue. Nuclei are longer and deeper staining. Many tumor giant cells are seen.

Clinically, and in the roentgenogram these neurogenic tumors bear a close resemblance to the lesions of the fibrospindle-cell series just discussed, though more pronounced destruction of bone is noted. As in the fibrospindle-cell tumors, there is a gradual transition among the

A conservative form of treatment is desirable in the majority of cases. Postoperative recurrences are frequent if surgical removal is employed too early (under 6 months), or if excision is inadequate.

There are isolated cases which have had successful regression of bone recurrence following therapeutic dosages of x-rays. Insufficient experience with this agent on myositis ossificans prevents any final evaluation of the results obtained.

7. *Hand-Schüller-Christian's Disease*.—This group of bone lesions is presented as an example of the so-called xanthomatoses involving congenital disturbances in lipid metabolism.<sup>1, 46, 48</sup> Organs connected with the reticuloendothelial system reveal a variety of changes. The disease usually makes its appearance early in life and is rarely seen after childhood. The clinical manifestations are variable. Exophthalmus, diabetes insipidus, pigmentation of the skin, and splenomegaly may be seen.

Bone changes are a constant finding and roentgenographically appear as large, rarefied defects, clearly demarcated in the skull and in other flat bones. Diffuse cystic areas may also be seen in the long bones with thinning of the cortex. There is no periosteal reaction.

The blood picture may show a severe anemia.

Histologically, large macrocytes, often binucleated, are the characteristic cells, together with eosinophiles, plasma cells, and lymphocytes. The lesions are quite radiosensitive and the affected bones often recossify under x-ray therapy. Great care must be exercised in giving the treatment to prevent overwhelming anemia. Transfusions are frequently indicated during the period of active roentgen therapy. Small divided doses are best tolerated.

#### COMMENT

The radiosensitivity of a tumor depends upon both the histologic characteristics of the tumor cells and the nature of the surrounding tumor bed.<sup>49</sup> It cannot be determined by microscopic examination alone. There are innumerable factors to be considered, some of which are not clearly understood at the present time.<sup>50, 51, 53</sup>

Practical knowledge of radiosensitivity has been gained by trial and error, correlating the effect of treatment upon the tumor cells, the variations in the surrounding medium of the tumor, and the ultimate results.

As treatment methods change, ideas of radiosensitivity are revised. Ideas of today may be obsolete tomorrow.

Radiosensitivity increases with the embryonal quality of the tumor or anaplastic changes in the tumor. This statement must be qualified immediately for those tumors which seem to have inherent radioresistant growth properties.<sup>50</sup>

The tumor bed is of great importance, and where cartilage and bone are concerned, two factors make for radioresistance: (1) very little

The roentgenographic picture is one closely resembling giant-cell tumor or polycystic disease of the bone. In addition, however, one may see isolated cysts beyond the main point of destruction. The trabeculae traversing the cystic cavities vary in density, more so than in giant-cell tumor.

These lesions at exploration show cystic destruction with or without vascular tissue lining the walls. The cysts contain fluid as a rule. The vascular tissue obtained is characteristic of angiomatous tissue elsewhere.

On reviewing the literature, one gains the impression that the majority of the angiomas of bone are of the cavernous type. In our cases, many showed the capillary type of angioma and 2 with proliferative changes suggested malignant change.

Angiomas affecting bone are essentially benign. They show varying degrees of radiosensitivity and the younger the patient the more effective the irradiation. This factor is also present in angiomas found in other parts of the body.

Isolated examples may be pointed out as having been cured by x-ray therapy alone or by surgical intervention.

6. *Recurrent myositis ossificans* may be divided into the traumatic and atraumatic forms arising about the thigh, arm, elbow, neck, and lumbar muscles.<sup>1, 44</sup>

Occupation played little or no role in the case histories studied. Injury was definitely an important factor in 60 per cent of the lesions.

The age incidence varied between 10 and 72 years.

The earliest physical sign after injury is the development of a soft, compressible mass which soon becomes indurated.

Bone may be detected in the roentgenogram within three weeks after the onset of the tumor formation. Small dense areas of calcification soon assume large proportions forming a large spicule of bone, usually separated from the shaft of the neighboring bone. Many lesions gain their maximum growth in six weeks or more and then spontaneously regress or become quiescent.

Histologically, degeneration of muscle, hyperplasia of connective tissue, and organization of hemorrhage are early findings, while osteoid tissue with marrow spaces, osteoblasts about spicules of bone, occasional islands of cartilage (30 per cent of cases), and benign myxomatous tissue represent fully developed myositis ossificans. Malignant changes may complicate myositis ossificans, but this is exceedingly rare.

Myositis ossificans progressiva,<sup>45</sup> a special form of the malady, usually begins in childhood; it affects the spinal muscles primarily. As the name implies, it eventually involves the muscles of the entire skeletal system.

A conservative form of treatment is desirable in the majority of cases. Postoperative recurrences are frequent if surgical removal is employed too early (under 6 months), or if excision is inadequate.

There are isolated cases which have had successful regression of bone recurrence following therapeutic dosages of x-rays. Insufficient experience with this agent on myositis ossificans prevents any final evaluation of the results obtained.

7. *Hand-Schüller-Christian's Disease*.—This group of bone lesions is presented as an example of the so-called xanthomatoses involving congenital disturbances in lipid metabolism.<sup>1, 46, 48</sup> Organs connected with the reticuloendothelial system reveal a variety of changes. The disease usually makes its appearance early in life and is rarely seen after childhood. The clinical manifestations are variable. Exophthalmus, diabetes insipidus, pigmentation of the skin, and splenomegaly may be seen.

Bone changes are a constant finding and roentgenographically appear as large, rarefied defects, clearly demarcated in the skull and in other flat bones. Diffuse cystic areas may also be seen in the long bones with thinning of the cortex. There is no periosteal reaction.

The blood picture may show a severe anemia.

Histologically, large macrocytes, often binucleated, are the characteristic cells, together with eosinophiles, plasma cells, and lymphocytes. The lesions are quite radiosensitive and the affected bones often reossify under x-ray therapy. Great care must be exercised in giving the treatment to prevent overwhelming anemia. Transfusions are frequently indicated during the period of active roentgen therapy. Small divided doses are best tolerated.

#### COMMENT

The radiosensitivity of a tumor depends upon both the histologic characteristics of the tumor cells and the nature of the surrounding tumor bed.<sup>19</sup> It cannot be determined by microscopic examination alone. There are innumerable factors to be considered, some of which are not clearly understood at the present time.<sup>50, 51, 53</sup>

Practical knowledge of radiosensitivity has been gained by trial and error, correlating the effect of treatment upon the tumor cells, the variations in the surrounding medium of the tumor, and the ultimate results.

As treatment methods change, ideas of radiosensitivity are revised. Ideas of today may be obsolete tomorrow.

Radiosensitivity increases with the embryonal quality of the tumor or anaplastic changes in the tumor. This statement must be qualified immediately for those tumors which seem to have inherent radioresistant growth properties.<sup>50</sup>

The tumor bed is of great importance, and where cartilage and bone are concerned, two factors make for radioresistance: (1) very little

reaction to irradiation by the individual cells; (2) an avascular type of tumor bed. Edema and infection also increase resistance.

It is certainly true that radiosensitivity does not parallel radio-curable. A cellular neoplasm such as Ewing's tumor is extremely sensitive to irradiation, yet the curability of the disease is far less striking. Of course, it may be argued that large doses of x-ray causing an initial favorable response but failing to sterilize the tumor show the resistant viability of the new growth. This introduces a different interpretation of the term radiosensitivity.

Tissue differentiation, resulting in growth restraint is a most important factor in altering the prognosis, despite the tumor's possible inherent radioresistance or sensitivity (Fig. 9).

CHART SHOWING THAT THE % OF FIVE YEAR CURES  
IS PROPORTIONAL TO  
THE TISSUE DIFFERENTIATION IN THE TUMOR

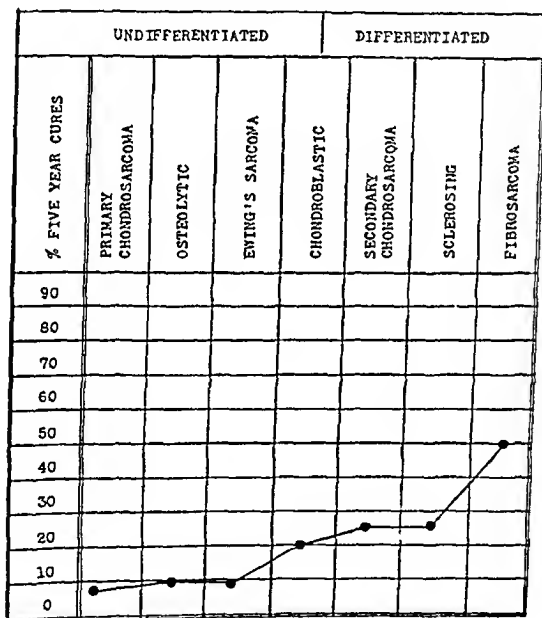


Fig. 9.—To illustrate the influence of tissue differentiation upon five-year survivals despite the radioresistance or multiple types of therapy used.

It is this underlying factor which permits repeated insults to certain tumors, and in spite of them, the patient survives in a number of instances.

Ferguson<sup>52</sup> in a recent publication decries early amputation and points out the number of cases of "osteogenic sarcoma" surviving, which frequently had late amputation often with preliminary x-ray treatment, repeated excisions, or partial resections before amputation was performed. He suggests the possibility that these procedures may have had a favorable influence upon the course of the tumor. I cannot accept this point of view.

If one separates osteogenic sarcoma into the various entities, detailed elsewhere in this paper, and considers the prognosis and treatment of each, and if one further considers the tissue differentiation of each, with its relative aggressiveness, it would seem that the following points are fundamental:

1. Regardless of the type of sarcoma, irradiation alone has rarely sufficed to accomplish a cure, while combined with resection it has offered better results.

2. Amputation is favored as a method of treatment.

3. Tumors with long preoperative symptoms are less aggressive in character and the patients survive in larger numbers.

4. Tumors with short preoperative symptoms usually connote a more aggressive process, with a reduction in case survivals.

5. The primary bone sarcomas which show the greatest tissue differentiation yield the largest percentage of cures when treated adequately.

6. Early diagnosis and aggressive treatment is to be recommended.

*Chondroma* and *osteochondroma* are radioresistant.

The various forms of *osteogenic sarcoma* are in general radioresistant. Nothing more than transient improvement in proved cases has been noted in the irradiation of these cases. We have observed an occasional sarcoma sterilized by x-ray treatment but the function of the extremity was also destroyed and, needless to say, surgery would have been more comfortable and adequate in the beginning.

Radiation is of advantage in those patients where palliation is desired or in technically inoperable locations.

*Chondroblastic sarcoma* is controlled by irradiation despite its inherent radioresistant qualities.

Many *giant-cell tumors* of bone are radiosensitive, though the tissue changes which occur are hard to explain. Overtreatment must be guarded against, as devitalized normal bone does not make for a satisfactory result.

Certain facts can be stated which seem to be closely related to failure in treating giant-cell tumor by irradiation or by surgery: (1) too early weight-bearing of the affected part; (2) perforation of the bone shell by the tumor before treatment is instituted; (3) inadequate therapy; (4) the declining healing power of bone due to age.

*Multiple myeloma* is moderately radiosensitive. The larger the area of bone destruction, the less satisfactory is the response. Palliation by moderate doses of irradiation is satisfactory, however, and partial sterilization of the tumor process may be obtained for awhile.

*Fibrosarcoma* is not usually radiosensitive and only very low grade malignant tumors may be controlled by escharotic doses of therapy.

Bone involvement by *metastatic carcinoma* may show marked palliative response to x-rays or radium.

*Angioma of bone* cannot be generalized upon, but isolated cases have been completely controlled by roentgen therapy.

Data on *recurrent myositis ossificans* are insufficient to recommend irradiation as a routine procedure.

*Hand-Schüller-Christian's disease* is quite sensitive to the x-rays and favorable results are the rule if the patient is kept under periodic and careful observation.

Many diseases not primary in bone but affecting it have not been mentioned. A sufficient variety has been presented, however, to illustrate the trend of treatment in the various groups.

#### REFERENCES

1. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, Am. J. Cancer 11: 667, 1936.
2. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, Internat. Surg. Dig. 10: 323, 1930.
3. Stewart, F. W., and Copeland, M. M.: Neurogenic Sarcoma, Am. J. Cancer 15: 1235, 1931.
4. Meyerding, H. W.: Exostosis, Radiology 8: 282, 1927.
5. Schramm, G.: Pathogenesis of Cartilaginous Exostoses and Enchondromas, Arch. f. Orthop. 27: 421-436, 1929.
6. Rixford, E.: Osteochondromatosis, Ann. Surg. 92: 673, 1930.
7. Ehrenfried, A.: Hereditary Deforming Chondroplasia; Multiple Cartilaginous Exostoses: A Review of the American Literature and Report of 12 Cases, J. A. M. A. 68: 502, 1917.
8. Hyndman, O. R.: Hereditary Deforming Chondrodysplasia: Report of a Case, Arch. Surg. 21: 12, 1930.
9. Jemna, G.: Multiple Chondromas of Bone, Riforma med. 45: 1445, 1929.
10. Geschickter, C. F.: Osteogenic Sarcoma, Arch. Surg. 24: 602, 798, 1932.
11. Bloodgood, J. C.: Bone Tumors, Myxoma, Central and Periosteal, Ann. Surg. 72: 712, 1920.
12. Coley, W. B., and Coley, B. L.: Primary Malignant Tumors of Long Bones, Arch. Surg. 13: 779, 1926; 14: 63, 1927.
13. Kolodny, A.: Bone Sarcoma, Surg., Gynec. & Obst. 44: 26, 1927.
14. Bloodgood, J. C.: Benign Bone Cysts, Osteitis Fibrosa, Ann. Surg. 52: 145, 1910; 56: 210, 1912; 69: 345, 1919.
15. Alexander, E. G., and Crawford, W. H.: Multiple Giant Cell Tumors, Ann. Surg. 86: 362, 1927.
16. Morton, J. J.: The Generalized Type of Osteitis Fibrosa Cystica, Arch. Surg. 4: 435, 1922.
17. Ballin, M., and Morse, P. F.: Parathyroidism, Am. J. Surg. 12: 403, 1931.
18. Merritt, E. A.: Irradiation of Parathyroids in Cystic Disease of Bones, J. A. M. A. 98: 1733, 1932.
19. Cutler, M., and Owen, S. E.: Irradiation of the Parathyroids in Generalized Osteitis Fibrosa Cystica, Surg., Gynec. & Obst. 59: 81, 1931.
20. Konjetzny, C. E.: Die sogenannte "lokalisierte osteitis fibrosa," Arch. f. klin. Chir. 121: 567, 1922.
21. Coley, W. B.: Malignant Changes in So-Called Benign Giant Cell Tumor, Am. J. Surg. 28: 768, 1935.
22. Simmons, C. C.: Malignant Changes Occurring in Giant Cell Tumor of Bone, Surg. Gynec. & Obst. 53: 469, 1931.
23. Bloodgood, J. C.: The Conservative Treatment of Giant Cell Sarcoma, Ann. Surg. 56: 210, 1912.
24. Ibid.: Benign Giant Cell Tumor of Bone: Its Diagnosis and Conservative Treatment, Am. J. Surg. 37: 105, 1923.
25. Geschickter, C. F., and Copeland, M. M.: Recurrent and So-called Metastatic Giant Cell Tumor, Arch. Surg. 20: 713, 1930.
26. Ibid.: Giant Cell Tumor and Osteitis Fibrosa Cystica, Arch. Surg. 19: 169, 1929.
27. Coley, B. L., and Higinbotham, N. L.: Surgical Treatment of Giant Cell Tumor, Ann. Surg. 103: 821, 1936.
28. Coley, B. L., and Higinbotham, N. L.: Solitary Bone Cyst: the Localized Form of Osteitis Fibrosa Cystica, Ann. Surg. 99: 432, 1931.
29. Herenden, R. E.: Radiation Therapy of Giant Cell Tumors of Bone, Treatment of Cancer and Allied Diseases, New York, 1940, Paul B. Hoeber, Inc., vol. 3, p. 2400.

30. Stewart, F. W.: Radiosensitivity of Tumors, *Arch. Surg.* 27: 1042, 1933.
31. Higinbotham, N. L.: The Surgical Treatment of Giant Cell Tumors of Bone, *Treatment of Cancer and Allied Diseases*, New York, 1940, Paul B. Hoeber, Inc., vol. 3, p. 2375.
32. Codman, E. A.: Epiphyseal Chondromatous Giant Cell Tumor of the Upper End of the Humerus, *Surg., Gynec. & Obst.* 52: 543, 1931.
33. Ewing, J.: A Review and Classification of Bone Sarcoma, *Arch. Surg.* 4: 485, 1922.
34. Copeland, M. M., and Geschickter, C. F.: Ewing's Sarcoma; The Nature of Ewing's Tumor, *Arch. Surg.* 20: 246, 421, 1930.
35. Morton, J. J.: The Treatment of Ewing's Sarcoma of Bone, *Treatment of Cancer and Allied Diseases*, New York, 1940, Paul B. Hoeber, Inc., vol. 3, p. 2422.
36. Coley, W. B.: Endothelial Myeloma or Ewing's Sarcoma, *Am. J. Surg.* 27: 7, 1935.
37. Geschickter, C. F., and Copeland, M. M.: Multiple Myeloma, *Arch. Surg.* 16: 807, 1928.
38. Batts, M., Jr.: Multiple Myeloma: Review of 40 Cases, *Arch. Surg.* 39: 807, 1939.
39. Pfahler, G. E.: The Roentgen Treatment of Metastatic Carcinoma of Bone, *Acta radiol.* 7: 280, 1926.
40. Witherspoon, J. I.: Roentgen Irradiation of Ovaries as Supplement to Surgical and Radium Therapy for Mammary Cancer, *Arch. Surg.* 33: 554, 1936.
41. Brunshung, A.: Observations on Administration of Large Doses of Calcium in Metastatic Carcinoma in Bone, *Am. J. Cancer* 25: 721, 1935.
42. Bucy, P. C., and Copp, C. S.: Primary Hemangioma of Bone With Special Reference to Roentgenologic Diagnosis, *Am. J. Roentgenol.* 23: 1, 1930.
43. Geschickter, C. F., and Maseritz, I. H.: Primary Hemangioma Involving Bones of the Extremities, *J. Bone & Joint Surg.* 20: 888, 1938.
44. Lewis, Dean: Myositis Ossificans, *J. A. M. A.* 80: 1281, 1923.
45. Chambers, T. E.: Myositis Ossificans: A Study of Another Unusual Case, *Arch. Surg.* 16: 755, 1928.
46. Rowland, R. S.: Xanthomatosis and the Reticulo-endothelial System, *Arch. Surg.* 42: 611, 1928.
47. Ibid: Christian's Syndrome and Lipoid Cell Hyperplasias of the Reticulo-endothelial System, *Ann. Int. Med.* 2: 1277, 1929.
48. Shelling, D. H., and Voshell, A. F.: Xanthomatosis Generalisata Ossium, *Arch. Int. Med.* 55: 592, 1935.
49. Ewing, J.: Tissue Reactions to Irradiation, *Am. J. Roentgenol.* 15: 93, 1926.
50. Failla, G.: Theory of the Biological Action of Ionizing Radiations, *Cancer Probl., Symposium*: p. 202, 1937.
51. Failla, G.: Some Aspects of the Biological Action of Ionizing Radiations, *Am. J. Roentgenol.* 44: 649, 1940.
52. Ferguson, A. B.: Treatment of Osteogenic Sarcoma, *J. Bone & Joint Surg.* 22: 96, 1940.
53. Ewing, J.: Factors Determining Radioresistance in Tumors, *Radiology* 14: 186, 1930.



# ASPIRATION BIOPSY

## FURTHER OBSERVATIONS WITH AN IMPROVED INSTRUMENT

FRANK WRENN, M.D., AND J. M. FEDER, M.D., ANDERSON, S. C.\*

(From the Department of Radiology and Pathology, the Anderson County Hospital)

AT THE outset, we visualized an appliance for the performance of aspiration biopsy that would furnish a section of tissue for study showing the various structures in continuity. This was in contrast to the methods then in use, their technique being based upon smear preparations of particles of tissue and the diagnosis made from cytologic appearance alone. We were willing to concede that in the hands of experts with long training in this type of observation satisfactory evaluations could be accomplished. This was of necessity not true in the case of the worker occasionally called upon to perform an examination by this method.

It was thought that an instrument patterned after a druggist's cork borer with the cutting edge serrated might prove of value if fitted with an exceptionally sharp trocar. After a suitable plug of tissue had been encircled, it was planned to imprison it within the lumen of the cannula and sever its attachment by twisting the syringe in such a manner that its base would be brought into contact with the sharp roughened edges of the instrument.

Proceeding with this idea in mind, a large bore spinal puncture needle was cut down, its cutting edge ground very sharp and in a serrated manner. Its stylet was likewise made exceptionally keen. For aspiration purposes a 10 c.c. record syringe was employed. We soon learned that it was essential to be in a position to lock the plunger of the syringe at the maximum excursion of its upstroke. After searching the market and finding such an appliance not to be available, one was extemporized by filing a notch on the shank of the plunger and having a spring catch placed upon the housing of the syringe barrel. With this rather crude extemporized outfit we were enabled to do fairly satisfactory work. About two years ago our original paper covering its application was published;<sup>1</sup> since that time with the aid of the research staff of Becton, Dickinson Co., Rutherford, N. J., a much more technically satisfactory instrument has been made generally available.

The principle behind our original idea has been adhered to, but the new device has many convenient improvements: among them is a thumb rest at the head of the stylet and a convenient finger rest beneath. An unusually sharp flat cutting edge has been placed upon the trocar. Thanks to the ingenuity of Dr. Oscar Schwidetzky, of Becton, Dickinson Co., a simple catch patterned after those used to hold umbrellas open

\*Received for publication, June 9, 1941.



Fig. 1-3. A typical case suitable for aspiration biopsy. The patient is a young woman and the lesion under investigation is a submaxillary tumor. Obviously, a cutting diaphragm operation would prove to be undesirable. 2. After the skin has been properly prepared and anesthetized, the meshed trocar and cannula are thrust through the wheal formed by the injection of the anesthetic and into the periphery of the tumor. The trocar is then removed and the syringe attached. 3. The instrument is driven several millimeters further into the tissue and vacuum is created by drawing syringe to maximum excursion where it is automatically locked. This vacuum is held for three minutes. The tissue plug is severed by a twisting motion, accomplished by turning syringe, bringing base of plug into cutting edges of cannula.

has been applied to the shaft of the plunger. It is very positive in action and simple to operate.

Our technique has remained unchanged from the original report but is summarized here:

1. A suitable antiseptic is applied to the skin area over the site of proposed puncture and a wheal is formed by novocain or other local anesthetic of choice.

2. The meshed trocar and cannula are thrust through the site of anesthesia and into the periphery of the tumor under investigation. (Some prefer to make a small nick with a knife before introducing the instrument. We feel that this is advantageous in certain areas, especially about the neck where sudden penetration of the needle under force might prove disastrous.)



Fig 2—Illustrating a commonly encountered potential pitfall in aspiration biopsy diagnosis. The specimen is a section cut from a breast tumor showing benign fibroadenoma in upper and right (R) aspect. In the lower left (L) it is definitely cancerous. Quite obviously, there is a possibility that material could be aspirated from the nonmalignant regions that would give an entirely false and dangerous impression. For this reason we have had forced upon us the decision to disregard negative evidence obtained in this manner, and when it is encountered to make further investigations. (Courtesy of Army Medical Museum, Washington, D. C., and Lieut. Col. J. R. Ash, Medical Corps, U. S. Army.)

3. The stylet is removed, the syringe attached, and the cutting edge of the cannula is pushed by using a gentle rotary movement several millimeters further into the site from which the biopsy is sought.

4. The vacuum is now drawn, the piston locked at its maximum excursion, and the cannula slightly advanced. We have found it advantageous to hold this vacuum for *three minutes* before attempting to free the tissue plug.

5. At the expiration of three minutes, an are is described with the syringe at a 45 degree angle in an endeavor to bring the plug of tissue into contact with the cutting edges of the cannula, thus severing it.

6. The instrument is withdrawn and the contents are expressed into normal saline solution. This solution should be used to flush the syringe and needle as at times the specimens may be recovered by this means when others fail. The advantage of this procedure is that specimens sufficiently large to fix, cut, stain, and mount in the usual manner are obtained. In another publication, we described in detail a technique for handling these small particles.<sup>3</sup> Martin and Ellis have aptly stated<sup>2</sup> that without a sympathetic attitude on the part of the pathologist no progress can be made in this rather difficult field of diagnosis. None of us wish to deny the fact that handling of these tissue fragments is difficult and time consuming.

#### SUMMARY

1. An improved instrument for taking aspiration biopsies is reported. No material change has been made in the technical procedure originally reported.

2. Aspiration biopsy is always a procedure of necessity, never of election. A number of years' experience has taught us that negative evidence is valueless and is disregarded in our final consideration of the case in question. Positive findings, on the other hand, are taken at face value.

3. We have found the application of this method especially valuable in lesions about the face and neck, especially in women by whom a cutting operation for diagnostic purposes would not be tolerated. Its value has been proved in the case of bone tumors also.

4. Aspiration biopsy is "the hard way." There is nothing easy about it, from the standpoint of either taking the specimen or tediously preparing the microscopic sections.

5. Extreme care must be used in the vicinity of great vessels and other vital structures as the instrument used is capable of inflicting serious damage.

#### REFERENCES

1. Wrenn, Frank, and Feder, J. M.: A New Instrument for Aspiration Biopsy, *South. M. J.* 32: 320-322, 1939.
2. Martin, Hayes E., and Ellis, Edward B.: Aspiration Biopsy, *Surg., Gynec. & Obst.* 59: 578-589, 1940.
3. Feder, J. M.: *Essentials of Applied Medical Laboratory Technic*, Charlotte, N. C., 1940, Charlotte Medical Press, pp. 220-223.

## THE USE OF A COLD AIR BLAST ON PRECANCEROUS SKIN LESIONS AND HEMANGIOMAS

J. K. POPPE, M.D., NEW HAVEN, CONN.

DRY carbon-dioxide ice in the solid form has been used very successfully for the treatment of small capillary hemangiomas in babies. Excision and sclerosing solutions have been used for the larger capillary and cavernous types of hemangiomas. A need has been felt for a modification of the freezing technique to be used on the medium-sized hemangiomas and those resistant to a single carbon-dioxide ice treatment. This direct application of carbon-dioxide ice to the skin, for more than ten seconds, over a small area causes a chemical burn with destruction of the skin and a permanent scarring. The use of radium may be objected to on the basis of the late carcinogenic action in these essentially benign lesions in babies.

A further need has also been felt for a simple, readily available method for removing precancerous, keratotic lesions from the skin, which will not cause a permanent scarring of the area. The radon bulb, which has long been used for the purpose, is not always available and is expensive to provide for only a few patients at a time. Electric cauteries and caustics, which are also effective for the lesions, tend to produce considerable scarring.

A method of freezing localized areas of skin and subcutaneous tissue of between 3 to 5 cm. in diameter to a depth of 0.5 to 1 cm., without causing a permanent destruction of the overlying epidermis, was worked out, as described.

### EQUIPMENT AND TECHNIQUE

A current of compressed air is blown through a coil of metal tubing packed in carbon-dioxide ice. A nozzle is placed on the end of the tubing by means of which the blast of air is played on the skin lesion to be treated. The compressed air is obtained from one of the hospital outlets to which the coil is attached by a piece of heavy rubber tubing securely fastened at each end. The air pressure in this institution is maintained at about eighty pounds per square inch. A section of  $\frac{3}{4}$  inch copper tubing, about 40 feet long, is wound into a convenient coil to fit in a standard-sized pail. About ten pounds of carbon-dioxide ice is then broken up and packed around the coil of pipe. Insulation

around the pail and over the ice will make it last much longer. A very short length of insulated hose is then used to connect a nozzle to the coil. This should not be more than 10 inches in length because of the rapid warming of the air in passing through it. A short piece of glass tubing drawn to a point can be used as a nozzle. The opening of the nozzle may vary from 2 to 4 mm. in diameter.

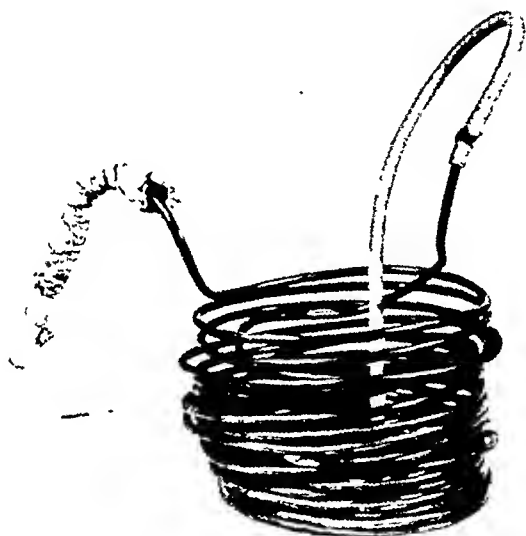


Fig. 1.—Coil of copper tubing with insulated nozzle used to cool the air blast.

If the apparatus is to be used to treat a number of patients successively, so that it will be operating over considerable periods of time, an intermediate drying chamber must be connected in the air hose before it enters the cooler. This is necessary in order to remove the moisture which would otherwise condense and freeze in the cooler, thereby obstructing the air flow, if used more than five to ten minutes at a time. Passing the air through a few centimeters of soda lime in an airtight chamber seems sufficient to dry it out adequately for this purpose.

Only a few seconds are required to cool off the apparatus sufficiently for use after the air has been turned on. A strong blast of cold air, which registers between  $-15$  and  $-20^{\circ}$  C., is directed on the lesion, the nozzle being held 1 to 3 cm. above the skin surface. The area frozen depends upon the size of the nozzle, the distance between the nozzle and the skin, and the time period during which the air is applied. A 0.5 cm. lesion can be treated over a 1 cm. area by holding a 2 mm. nozzle about 1 cm. above the skin surface for twenty seconds.

## THE USE OF A COLD AIR BLAST ON PRECANCEROUS SKIN LESIONS AND HEMANGIOMAS

J. K. POPPE, M.D., NEW HAVEN, CONN.

DRY carbon-dioxide ice in the solid form has been used very successfully for the treatment of small capillary hemangiomas in babies. Excision and sclerosing solutions have been used for the larger capillary and cavernous types of hemangiomas. A need has been felt for a modification of the freezing technique to be used on the medium-sized hemangiomas and those resistant to a single carbon-dioxide ice treatment. This direct application of carbon-dioxide ice to the skin, for more than ten seconds, over a small area causes a chemical burn with destruction of the skin and a permanent scarring. The use of radium may be objected to on the basis of the late carcinogenic action in these essentially benign lesions in babies.

A further need has also been felt for a simple, readily available method for removing precancerous, keratotic lesions from the skin, which will not cause a permanent scarring of the area. The radon bulb, which has long been used for the purpose, is not always available and is expensive to provide for only a few patients at a time. Electric cauteries and caustics, which are also effective for the lesions, tend to produce considerable scarring.

A method of freezing localized areas of skin and subcutaneous tissue of between 3 to 5 cm. in diameter to a depth of 0.5 to 1 cm., without causing a permanent destruction of the overlying epidermis, was worked out, as described.

### EQUIPMENT AND TECHNIQUE

A current of compressed air is blown through a coil of metal tubing packed in carbon-dioxide ice. A nozzle is placed on the end of the tubing by means of which the blast of air is played on the skin lesion to be treated. The compressed air is obtained from one of the hospital outlets to which the coil is attached by a piece of heavy rubber tubing securely fastened at each end. The air pressure in this institution is maintained at about eighty pounds per square inch. A section of  $\frac{3}{8}$  inch copper tubing, about 40 feet long, is wound into a convenient coil to fit in a standard-sized pail. About ten pounds of carbon-dioxide ice is then broken up and packed around the coil of pipe. Insulation

## RESULTS

A pitted, frozen plaque is immediately formed. This disappears in a few minutes, leaving an erythematous area which may become crusted over in two or three days if the treatment has been more than twenty seconds. This crust usually falls off within ten or twelve days, permitting a second treatment to be given within two weeks, if indicated.



Fig. 2.—Keratotic lesions on dorsum of right hand and forearm of Patient 1 before treatment. This patient developed a large squamous-cell carcinoma on the dorsum of the left hand from a similar lesion.

Experimental use of this method on rabbits' ears and abdomens showed that a maximum treatment of any single area should not be more than sixty seconds to avoid destruction of the skin and damage to the deep tissues. Treatment of from three to five minutes caused an ulceration which extended through the entire thickness of a rabbit's ear or caused peritonitis, if used on the abdomen.

## COMMENTS

The results obtained by this method of indirect freezing of precancerous skin lesions have been very successful, with complete disappearance of the treated lesions in all but one case (Case 12).



TABLE I  
RESULTS OF AIR BLAST TREATMENTS ON PRECANCEROUS SKIN LESIONS\*

NO.	NAME	LESION			TREATMENT		RESULT	
		LOCATION	SIZE	NO.	TIME (IN SECONDS)	NO.	TIME (AFTER TREATMENT)	LESION
1	C. W.	Dorsum (right hand)	3.0 cm.	4	45	2	4 wk.	Disappeared
2	C. O.	Left forearm	3.0 cm.	3	45	2	4 wk.	Disappeared
3	J. M.	Right ear	0.5 cm.	1	20	1	2 wk.	Disappeared
4	H. B.	Nose	0.5 cm.	1	18	1	4 wk.	Disappeared
5	A. E.	Face	0.5 cm.	1	20	1	4 wk.	Disappeared
6	R. H.	Forearms	1.0 cm.	3	20	1	4 wk.	Disappeared
7	C. K.	Face	0.8 cm.	5	20	1	4 wk.	Disappeared
8	T. O.	Face	1.0 cm.	1	25	1	4 wk.	Disappeared
9	J. O.	Cheek	2.0 cm.	1	37	1	4 wk.	Disappeared
10	M. P.	Face	0.8 cm.	2	25	1	4 wk.	Disappeared
11	H. R.	Forehead	0.5 cm.	1	20	1	4 wk.	Disappeared
12	J. S.	Ear	0.5 cm.	1	20	1	8 wk.	Unchanged
13	M. T.	Hand, shoulder, and chest	2.0 cm.	1	30	1	6 wk.	Disappeared
14	E. R.	Forehead	0.8 cm.	1	25	1	2 wk.	Disappeared

\*Lesions treated, 28; lesions cured, 27.

\*Lesions treated, 28; lesions cured, 27.

TABLE II  
RESULTS OF AIR BLAST, SUPPLEMENTED WITH DRY ICE TREATMENTS, ON HEMANGIOMAS IN CHILDREN

NO.	NAME	LESION			TREATMENT			RESULT		
		NO.	TYPE	SIZE	LOCATION	TYPE	TIME	NO.	TIME	RESULT
1	F. B.	1	Capillary	2 by 2.5 cm.	Right buttock	Air	20 sec.	1	3 wk.	Blanched
2	L. C.	1	Port wine	3 by 4 cm.	Right cheek	Ice	10 sec.	2	8 wk.	Disappeared
3	E. R.	1	Capillary	1.5 by 3 cm.	Anteauricular	Air	25 sec.	6	16 wk.	Blanched
4	W. B.	1	Port wine	3 by 5 cm.	Right cheek	Air	25 sec.	3	6 wk.	Disappeared
5	J. K.	1	Capillary	2 by 3 cm.	Right leg	Air	30 sec.	3	10 wk.	Disappeared
6	B. W.	1	Capillary	1.5 by 2 cm.	Left leg	Air	60 sec.	1	6 wk.	Improved
7	M. F.	3	Capillary	1.5 by 2.5 cm.	Abdomen	Air	20 sec.	2	6 wk.	Cured
				1.5 by 2 cm.	Right arm	Air	20 sec.	3	10 wk.	Cured
				1 by 0.5 cm.	Back	Air	20 sec.	3	10 wk.	Cured

of a large lesion with small amounts of carbon-dioxide ice, after the main body of the hemangioma has disappeared following a single air blast treatment.

Several attempts have been made to treat port-wine marks by this method with only moderate success. A certain amount of blanching occurs over the treated area without any scarring, which is a definite improvement over direct treatment with dry ice. No complete disappearance of a port-wine mark has, as yet, been noted.

#### CONCLUSION

1. The indirect freezing of large hemangiomas and precancerous skin lesions by an air blast is a relatively simple and economical method of removing these lesions.

2. A definite advantage over the more caustic agents is present in that the residual skin defect is minimal compared with that resulting from the other methods mentioned.

This particular lesion originated from freezing the ear a number of years previously which may account for its intractability to further freezing treatment. The only cases listed here are those in which an adequate follow-up has been obtained, although a much larger number of precancerous lesions have been treated. Several of these patients have had one or more skin cancers which have already developed from similar keratotic lesions. Precancerous lesions near the eye should not be treated by air because of the ecchymosis produced in this region.



Fig. 3.—The right hand and forearm of the same patient four months after treatment with the cold air blast.

The use of this method has been restricted to the larger hemangiomas, and the results on these lesions have been superior to those previously obtained with repeated application of solid carbon-dioxide ice. The superior results obtained by this method are due to the larger area which can be covered during a single treatment with less ulceration, crusting, and subsequent scarring. Several mothers who have seen the results of both types of treatment have requested the air blast in preference to the dry ice in view of its minimal reaction on the skin. It is occasionally necessary to touch up small pseudopodia around the edges

## CASE REPORTS

CASE 1.—Wm. K., an 8 year old white boy, was admitted to the University Hospital on Dec. 26, 1938. One month previously he had sustained a compound skull fracture in the right frontal region. The wound was débrided but became infected and a fungus developed (Fig. 1).



Fig 1—Cerebral fungus in right frontal region before grafting

The general and neurological examinations were essentially negative except for the local lesion. The intracranial pressure was normal. The fungus had been dressed for some time with plain sterile gauze. When admitted to the hospital the dressings were removed and a fair bed of granulation tissue was noted to have developed on the fungus. The herniation was considerable and by palpation the impression was obtained that the anterior aspect of the right ventricle might be sufficiently superficial to be opened if amputation of the fungus were undertaken. There appeared to be no reason why small skin grafts would not take on the granulations. On Dec. 28, 1938, the entire surface was covered with small deep grafts. Eighty per cent of the grafts took readily. A few in the center of the fungus died. Two more attempts to graft this small area were partially successful and by Feb. 19, 1939, at which time the patient was discharged, epithelization was complete. While epithelization was in progress, the hernia spontaneously receded until it was flat.

# TREATMENT OF MAJOR WOUNDS OF THE SKULL

## I. CEREBRAL FUNGUS: TREATMENT BY SKIN GRAFTING

OLAN R. HYNDMAN, M.D., IOWA CITY, IA.

*(From the Department of Surgery, Neurosurgical Service, College of Medicine, State University of Iowa)*

**I**F A major cranial defect is sustained so that an area of cerebrum one inch or more in diameter is exposed and becomes infected, a herniating mass of infected and inflamed brain tissue will usually ensue. The infected hernia cerebri is commonly referred to as a fungus. I feel certain that the lesion is not nearly so common now in civil life as it was twenty years ago in spite of the increasing incidence of head injuries. This fact in itself is evidence for the increasingly better management of acute head injuries. Nevertheless an occasional fungus appears to be unavoidable, and in war surgery the lesion is a relatively prominent one. After having developed, it presents itself as a real problem. The fungus is highly intractable to treatment and often it ultimately leads to fatality. The surgeon is sooner or later tempted to amputate the herniating mass flush with the skull, only, as in the case of the Lernaean hydra, to be confronted by a recurrence, if, indeed, death is not precipitated by meningitis, ventriculitis, or an overwhelming encephalitis.

The histologic evidence of inflammation extends to varying depths from the fungus into the brain. This localized encephalitis with the associated edema and swelling progress in a vicious cycle. This lesion in which there is an absence of skin with exposure of underlying tissues is unique when brain is the underlying tissue. The most important factor which makes the lesion unique is the poor grade of granulation tissue over which epithelium might grow. The only source of granulation tissue from the brain is the fibroblast of the walls of vessels and these are relatively sparse. This fact combined with the slow but progressive herniation of the fungus makes it understandable why epithelium does not grow in from the skin margin as it does in the case of open wounds elsewhere.

It has hitherto been a custom and almost a dictum in neurological surgery that exposed brain should not be covered with gauze but by some smooth tissue such as gutta serena and this type of dressing was used in World War I.<sup>1</sup> Such a dressing does not encourage the development of granulations. Although the source of granulation tissue is deficient, nevertheless a good bed of granulations can be provoked by a dressing of dry gauze as is done in the case of other wounds. Such a bed of granulations has proved to be adequately receptive for small deep skin grafts in two consecutive cases followed by rapid and complete healing

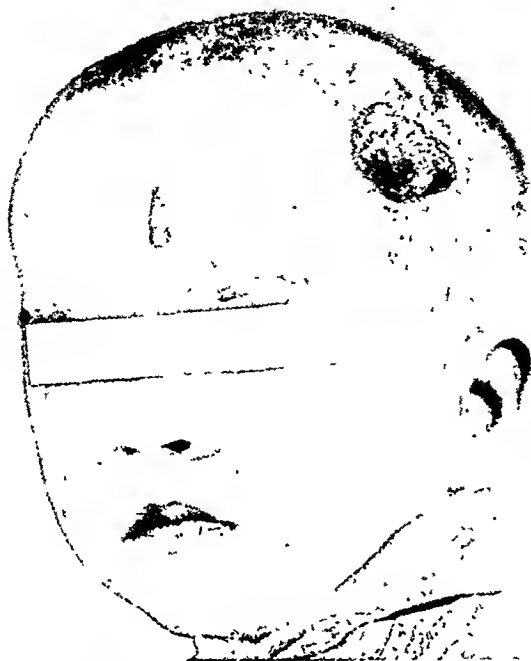


Fig. 3.—Cerebral fungus before grafting.



Fig. 4.—Photograph of cerebral fungus shown in Fig. 3 taken eight days following the application of small deep grafts. Epithelialization is complete and the herniation has completely receded.

The patient returned on March 21, 1939, the wound being completely healed. A photograph was taken at this time (Fig. 2). The wound has remained healed to the time of writing (two years).



Fig. 2.—Photograph of cerebral fungus shown in Fig. 1 taken three months later, showing complete epithelization. The hernia receded spontaneously after it was grafted.

CASE 2.—Wm. McH.,\* a white boy, 4 years of age, was admitted to the Children's Hospital of Cincinnati on July 20, 1940. Six weeks before he had fallen from a swing, striking his head. Osteomyelitis and brain abscess developed. The abscess was drained through an opening in the frontal cranium measuring about  $1\frac{1}{2}$  by 1 inch. A fungus developed as shown in Fig. 3. The fungus was dressed with gauze, and when the granulations were sufficiently abundant, they were covered by small deep grafts. In eight days the fungus was flat and epithelization complete (Fig. 4).

Before grafting, the patient exhibited an increased intracranial pressure as evidenced by papilledema. A ventriculogram revealed some dilatation of the third and lateral ventricles. Dr. Evans interpreted the situation as one of obstructive hydrocephalus and felt that this was largely responsible for the herniation of the fungus. Concomitant with grafting, therefore, he made a perforation in the third ventricle

\*This patient developed a cerebral fungus while on the neurosurgical service of Dr. Joseph Evans, the Children's Hospital, Cincinnati, Ohio. Dr. W. T. McElhinney, having studied Case 1 as a student at the State University of Iowa, suggested that the same methods be applied to Case 2. Prompt healing followed. I am indebted to Drs. Evans and McElhinney for kindly permitting me to include their case in this publication.

healing but probably will forestall complications that may attend delayed healing. All efforts leading to skin grafting as a final stage in treatment would seem to be in order.

#### CONCLUSIONS

1. Granulations may be induced on a fungus cerebri that will be adequately receptive to small deep skin grafts.

2. To this end granulations should be encouraged by dressing the herniated brain with gauze rather than an inert material such as gutta serena.

3. The fungus should not necessarily be amputated. The herniation will recede when epithelization is complete.

#### REFERENCES

1. Horrax, Gilbert: A Proposal for the More Radical Treatment of Gunshot Wounds of the Brain, *Canad. M. A. J.* 43: 320-324, 1940.
2. Proceedings of the Twenty-seventh Meeting of the Society of British Neurological Surgeons, *J. Neurol. & Psychiat.* 3: 342-352, 1940.



for the purpose of shunting the ventricular fluid into the basilar subarachnoid spaces. It is the opinion of Dr. Evans that this procedure was responsible for the retraction of the fungus as well as the subsequent recession of the increased intracranial pressure and would not attribute the recession to epithelization alone. I am at variance with this view as brought out in the discussion.

#### DISCUSSION

The two cases reported here illustrate a simple and effective method of treating cerebral fungus. Granulations can be induced on the fungus which will be receptive to skin grafts. A good method of provoking abundant and healthy granulations is the application of plain sterile gauze and this dressing is therefore preferable to gutta serena. Small deep grafts should be used and applied close together covering the entire surface of the fungus. In Case 1 the fungus receded spontaneously as epithelization progressed. It is my opinion that the local encephalitis with its associated edema subsides when epithelization occurs, thus accounting for the retraction of the hernia. The prompt subsidence of infection and its attending signs and symptoms when large areas over the body are grafted is a common observation.

Undoubtedly the end result of a healed fungus involves a firm attachment of scarred brain to skin at the site of the defect. This scar in some cases may later lead to the development of epileptic seizures. However, in such an event and when the infection has subsided, the scar may be repaired in the accepted manner with impunity. The objective in treating the fungus is to save the patient's life.

Upon the completion of this report Dr. Wilder Penfield called my attention to the Proceedings of the Twenty-seventh Meeting of the Society of British Neurological Surgeons.<sup>2</sup>

In a discussion of the treatment of penetrating wounds of the skull, consideration is given by Cairns to the problem of cerebral fungus. The conditions leading to and maintaining a fungus are discussed. In the event that a fungus develops, it is important to establish the presence or absence of complicating factors that might be associated with the fungus, such as abscess or some degree of meningitis. Cairns advocates the use of ventriculography to gain information concerning the possibility of abscess and wisely cautions against needling the fungus unless a ventriculogram reveals the presence of an expanding mass near it. O'Connell points out that the uncomplicated fungus is associated with a quite high protein content in the spinal fluid and a very low or slight pleocytosis.

Wright and Clark-Maxwell report good results from skin grafting the fungus and endorse the method as ideal treatment.

The experience with the cases reported in this paper coincides, therefore, with the experience of the British surgeons. Skin grafting is indicated as treatment of a fungus and not only will greatly hasten its

of the neck with a coxa valga deformity is never impacted if the line of fracture is nearly vertical or greater than 30 degrees with the horizontal. Pressure forces between the two fragments must dominate in an impacted fracture. When shearing forces are greater than pressure forces between the two fragments, the fracture cannot be considered impacted.

The true impacted fracture of the hip unites by bony union without any special form of internal or external immobilization. If the fracture is not impacted, operative internal fixation is essential. Impaction is synonymous with mechanical features which favor the domination of pressure forces over shearing forces from transmission of body weight and muscle contraction. An abduction injury with abduction of the distal neck and shaft fragment in relation to the proximal head fragment, coxa valga deformity, an almost horizontal subcapital fracture line as seen in the anteroposterior radiogram, no displacement as seen in the true lateral radiogram, and a fractured limb that can be moved freely and almost painlessly, are the radiographic and clinical features which should be essential in the universal definition of an "impacted fracture" of the hip.

—*Vernon L. Hart, M.D.*

Minneapolis, Minn.

# Editorial

---

## Impacted Fracture of the Hip

**W**HEN is a fracture of the neck of the femur impacted? The term "impacted fracture" of the hip is used frequently by physicians. Unfortunately, the term is too frequently misused. The physician who is responsible for the treatment of the patient and the roentgenologist who assists the physician in the proper interpretation of the x-ray studies of the fractured hip should use the same definition of the term "impacted fracture." If there could be an accepted definition of the term by the profession there would be less confusion, less morbidity, and a greater appreciation of the mechanical principles that are involved in the treatment and in the prognosis of fractures of the neck of the femur.

A true impacted fracture of the neck of the femur always unites by bony union without any special treatment. Nailing operations or any of the other types of operative internal fixation, which are so important in the treatment of fractures of the neck of the femur that are not impacted, are contraindicated. It is, therefore, most important for all of us to accept and teach one and only one definition of the term "impacted fracture."

This fracture presents constant clinical subjective and objective findings and specific radiographic features. Clinically, the fractured extremity can be moved freely and almost painlessly. The patient may even walk after the injury. The severe pain, muscle spasm, external rotation deformity, shortening, and almost complete loss of function of the limb which characterizes the fracture of the hip that is not impacted, are not present. Radiologically, the fracture line through the neck of the femur is subcapital, almost horizontal, and the neck and shaft of the femur are abducted in relation to the head. The normal angle of head, neck, and shaft is increased and a coxa valga deformity is present. The lateral radiogram shows no displacement between the head and neck fragments. These radiographic findings are essential in the diagnosis of "impacted fracture." The fracture is impacted because the mechanical forces between the two fragments are pressure forces and not shearing forces. There is never a true impaction if the normal angle between the two fragments is diminished with a coxa vara deformity because the forces between the fragments are then shearing and not pressure forces. Internal fixation is essential in the treatment of a fractured femoral neck with coxa vara deformity or when the neck and shaft fragment are adducted in relation to the head fragment. All fractures with a coxa valga deformity are not impacted, but all impacted fractures are in a coxa valga position. An abduction fracture

## PHARMACOLOGIC AND PATHOLOGIC CONSIDERATIONS

Pentothal sodium, or sodium ethyl (1 methylbutyl) thiobarbiturate, owes its success as an anesthetic agent to the fact that like evipal it belongs to the group of so-called "light" or short-acting barbiturates.<sup>28, 80</sup> The "heavy" barbiturates, such as nembutal and sodium amytal, remain unchanged in vivo and are excreted as such by the kidneys for as long as seventy-two hours. For this reason, when they are used as anesthetic agents, there is an undesirable prolongation of the anesthetic effect. Although the method of the destruction of pentothal in the body is not clearly understood, it has been shown that the process occurs so rapidly that scarcely a trace can be found in secretions three to twelve hours after the administration of single therapeutic doses, and for all practical purposes the effect lasts but three to thirty minutes, depending upon the dose which is used.<sup>16, 80, 174</sup> However, after prolonged administration the rate of detoxification is not proportionate to the total dosage, as shown by Kohn-Richards and Grimes,<sup>87</sup> who demonstrated that the rate of detoxification of pentothal given to rabbits by continuous infusion is roughly one-half that after a single dose. Similar results were obtained in an experimental study performed by Kozelka and Hine.<sup>89</sup> Gruhzit and co-workers<sup>86</sup> suggest that normal organs are able to destroy only a limited amount of pentothal or that the organs are so altered by the drug that they lose their capacity for detoxification. Butler and Bush<sup>24, 25</sup> offer experimental evidence that some short-acting barbiturates are transformed in vivo to less active compounds which have a more prolonged but less intense action. Either of these explanations helps clarify clinical and experimental observations of the prolonged and variant effects of large doses of pentothal.

The pharmacologic action of pentothal sodium has been subjected to close scrutiny by numerous investigators.<sup>7, 9, 11, 15, 16, 22-27, 29-31, 39, 52-56, 59, 64, 71, 82, 86, 88-90, 103, 107-109, 116, 123, 124, 129, 131, 135, 146, 147, 153, 155, 156, 159, 161, 162, 164, 172, 177, 179, 182, 186, 62, 197-200</sup> Its effects upon the circulatory system are minimal, no significant changes having been observed clinically in the pulse volume and rate, the blood pressure,<sup>30, 31, 82, 116</sup> or electrocardiographic tracings.<sup>15, 29, 30, 86, 116, 159, 182, 197</sup> The occasional appearance of conduction changes, as indicated by ectopic beats,<sup>25</sup> has been explained on the basis of a transitory anoxemia, the relief of which causes the resumption of normal rhythm. Cardiac irregularities, already present, have not been affected by sodium pentothal anesthesia.<sup>182, 197</sup> The well-recognized vasodilatation which accompanies administration of pentothal has been utilized in diagnostic tests for peripheral vascular disease<sup>192</sup> and as a prognostic agent in the preoperative consideration of essential hypertension.<sup>14</sup>

Investigations by Reynolds and Veal<sup>133, 134, 136, 137</sup> suggest the possibility that continuous administration of small amounts of pentothal

# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## INTRAVENOUS PENTOTHAL SODIUM ANESTHESIA

### A REVIEW OF THE LITERATURE

CARROLL H. LONG, M.D., AND ALTON OCHSNER, M.D., NEW ORLEANS, LA.  
(From the Department of Surgery, School of Medicine, Tulane University)

THE successful use of pentothal sodium as an intravenous anesthetic by numerous groups, and its recommendation by some as "one of the most valuable advances in the science of anesthesia that has been made in recent times,"<sup>116</sup> makes a thorough consideration of this agent mandatory upon progressive anesthetists and upon surgeons who assume part of the responsibility of directing the anesthetic control of their patients. This review is made in an attempt to evaluate this anesthetic agent. Since it is the opinion of many pharmacologists that there is slight hope of producing additional effective members of the barbiturate group,<sup>3</sup> pentothal sodium may remain the barbiturate most acceptable for anesthesia.

Various intravenous anesthetic agents had been used prior to the introduction of sodium pentothal.<sup>28, 60, 64, 65, 102</sup> The first recorded use of intravenous anesthesia appears to be that of Pirogoff and von Flour, who, in 1847, administered ether in this way, but abandoned the method because of the high mortality. Ore, in 1872 at Lyons, used a solution of ethyl chloral hydrate. Remarkable results were obtained by the Russian, Federow, who, during the early years of the twentieth century, reported the intravenous use of 0.75 per cent hedonal for anesthesia in 530 cases without a death. At a later date, Gwathmey<sup>58</sup> used from 5 to 7.5 per cent ether in Ringer's solution intravenously and later reported the use of trichlorisopropyl alcohol intravenously. Other drugs which have been suggested as intravenous anesthetic agents at various times include chloroform, morphine sulfate, paraldehyde, and avertin.

The barbituric acid compounds were first introduced as intravenous anesthetic agents in 1929 when an attempt was made to utilize sodium amytal. This drug was abandoned because of the lack of proper relaxation, the postoperative restlessness, and the prolonged recovery period. Although pentothal sodium had been developed earlier, by Tabern and Volwiler,<sup>179</sup> it first was used clinically by Lundy at the Mayo Clinic during the latter six months of 1934.<sup>2, 106, 178</sup> Since that time he and others have reported its use in 54,851 cases with almost universal praise of its anesthetic properties.

## PHARMACOLOGIC AND PATHOLOGIC CONSIDERATIONS

Pentothal sodium, or sodium ethyl (1 methylbutyl) thiobarbiturate, owes its success as an anesthetic agent to the fact that like evipal it belongs to the group of so-called "light" or short-acting barbiturates.<sup>28, 80</sup> The "heavy" barbiturates, such as nembutal and sodium amytal, remain unchanged in vivo and are excreted as such by the kidneys for as long as seventy-two hours. For this reason, when they are used as anesthetic agents, there is an undesirable prolongation of the anesthetic effect. Although the method of the destruction of pentothal in the body is not clearly understood, it has been shown that the process occurs so rapidly that scarcely a trace can be found in secretions three to twelve hours after the administration of single therapeutic doses, and for all practical purposes the effect lasts but three to thirty minutes, depending upon the dose which is used.<sup>10, 80, 174</sup> However, after prolonged administration the rate of detoxification is not proportionate to the total dosage, as shown by Kohn-Richards and Grimes,<sup>87</sup> who demonstrated that the rate of detoxification of pentothal given to rabbits by continuous infusion is roughly one-half that after a single dose. Similar results were obtained in an experimental study performed by Kozelka and Hinc.<sup>69</sup> Gruhzit and co-workers<sup>76</sup> suggest that normal organs are able to destroy only a limited amount of pentothal or that the organs are so altered by the drug that they lose their capacity for detoxification. Butler and Bush<sup>24, 25</sup> offer experimental evidence that some short-acting barbiturates are transformed in vivo to less active compounds which have a more prolonged but less intense action. Either of these explanations helps clarify clinical and experimental observations of the prolonged and variant effects of large doses of pentothal.

The pharmacologic action of pentothal sodium has been subjected to close scrutiny by numerous investigators.<sup>2, 9, 11, 15, 16, 22-27, 29-31, 39, 52-56, 59, 64, 71, 82, 86, 88-90, 107, 107-109, 116, 121, 125, 129, 131, 135, 140, 147, 153, 155, 156, 159, 161, 162, 164, 172, 177, 179, 182, 186, 92, 197-200</sup> Its effects upon the circulatory system are minimal, no significant changes having been observed clinically in the pulse volume and rate, the blood pressure,<sup>10, 31, 52, 116</sup> or electrocardiographic tracings.<sup>15, 29, 39, 86, 116, 179, 182, 197</sup> The occasional appearance of conduction changes, as indicated by ectopic beats,<sup>51</sup> has been explained on the basis of a transitory anoxemia, the relief of which causes the resumption of normal rhythm. Cardiac irregularities, already present, have not been affected by sodium pentothal anesthesia.<sup>182, 197</sup> The well-recognized vasodilatation which accompanies administration of pentothal has been utilized in diagnostic tests for peripheral vascular disease<sup>160</sup> and as a prognostic agent in the preoperative consideration of essential hypertension.<sup>11</sup>

Investigations by Reynolds and Veal<sup>173, 174, 177</sup> suggest the possibility that continuous administration of small amounts of pentothal

sodium may result in heart muscle poisoning. To a series of dogs they gave repeated minimal narcotic doses, finding that there was a progressively longer narcotic effect after each injection. In every instance, death followed a sudden drop in blood pressure to zero, a termination which occurred without warning and in the absence of respiratory paralysis. The suddenness of the blood pressure fall and the previous appearance of ectopic ventricular contractions suggested to the authors the development of ventricular fibrillation. The several reports of this group of experiments make no mention of any control of fluid balance or of oxygenation, and for this reason judgment must be withheld as to the validity of the conclusions drawn by the authors. It is Mousel's opinion<sup>128</sup> that cardiovascular collapse is secondary to anoxemia caused by prolonged respiratory arrest. No such occurrence of cardiac failure during pentothal anesthesia is recorded in the clinical reports.

Pentothal sodium causes a very definite respiratory depression which is clearly demonstrated by a shallowness of breathing without change in the respiratory rate. Clinically, respiration is likely to be almost imperceptible so that methods of evaluating the depth of anesthesia other than observation of the respiration must be relied upon. This depression of respiration is dependent upon the concentration of the drug in the blood at any one time so that large amounts may be given safely in broken doses over a period of time.<sup>16</sup> Fortunately, the rate of destruction of the drug given in therapeutic doses is so rapid that even though depression of respiration results in momentary arrest, breathing recurs almost before cyanosis appears. Adriani and Rovenstine<sup>10</sup> have shown experimentally that pentothal as well as other anesthetic agents produces a constriction of the bronchial musculature, probably through parasympathetic stimulation, which is relieved by atropine.

Weese,<sup>198</sup> in calling attention to a number of deaths reported during operation for sublingual infections under various intravenous barbiturate anesthetics, advances the following interesting explanation on the basis of experimental work performed with dogs. Infection in the area of the carotid sinus, which normally exerts an inhibitory effect on the respiratory center, increases the sensitivity of this structure by impairing its blood supply. Under these circumstances, the fast acting intravenous barbiturates anesthetize the central nervous system more rapidly than the carotid sinus. If the carotid sinus is traumatized by operation begun during this phase of anesthesia, such powerful inhibition of the respiratory center may result that death ensues. Weese advises that anesthesia continue for at least five minutes before the beginning of any operative procedure for infection in the neck so that sufficient time will be allowed for the anesthetizing of this portion of the vagus system.

Whereas the final disposition of pentothal in the body has never been clearly demonstrated, it has been assumed that it is detoxified in the

liver. The clinical and experimental data which have been presented as a basis for this assumption, however, have been not entirely convincing. Three cases of jaundice following pentothal anesthesia have been reported. Vaizey<sup>180</sup> suggested that in his case the phenomenon may have been a superimposed catarrhal jaundice; Phillips<sup>142</sup> reported two cases of jaundice "which might be attributed to pentothal." Several anesthetists<sup>123, 129</sup> report cases in which pentothal administered to patients with known hepatic damage caused prolonged periods of anesthesia. Experimental poisoning of the liver with hepatotoxins, such as chloroform and carbon tetrachloride, gives to therapeutic doses of short-acting barbiturates long-acting anesthetic action.<sup>9</sup>

Reynolds, Sehenken, and Veal,<sup>153, 154</sup> after giving comparatively large doses of pentothal sodium to mice, found areas of focal necrosis in the livers of nineteen out of twenty animals, a change which also was present after nembutal anesthesia but absent after the administration of amytal and evipal. Again these authors make no mention of metabolic control or oxygenation during anesthesia. Other<sup>30, 71, 80</sup> investigators in experiments upon mice, dogs, and monkeys have found no liver changes other than the mobilization of glycogen and its temporary replacement by fatty infiltration, a change which occurs in all general anesthesia.

Ravdin<sup>149</sup> states that liver necrosis is likely to occur when any of a variety of anesthetic agents are used, regardless of the glycogen level, if the liver fat is above normal or the reserve stores of protein are seriously reduced. Since in hepatic disease there is impaired flow of blood, anoxia of the liver results easily. Adequate oxygenation minimizes this danger. It is his opinion that extensive liver damage occurs during ether anesthesia when the oxygen supply is reduced to 15 per cent, a concentration 5 per cent less than air, and that death frequently is caused by anoxemia during anesthesia. Lahey<sup>93</sup> states that "anoxemia is the basis of most of the anesthetic difficulties."

Scheiffley and Higgins<sup>161</sup> called attention to the possibility that hepatotoxins may alter the central nervous system as well as the liver. An experiment was devised in which they removed 70 per cent of the liver of each of a group of nine rats and observed that the duration of the action of pentothal sodium was not influenced by this partial hepatectomy. They found also that unilateral nephrectomy did not affect the action of the drug. This method of approach would seem to obviate the objections to the use of the hepatotoxins in determining the action of pentothal upon the liver and to corroborate the clinical observations of other observers that patients with hepatic damage require full doses of pentothal sodium for narcosis.<sup>9</sup> This form of anesthesia has been used in cases of intense jaundice,<sup>9</sup> in massive carcinoma of the liver,<sup>170</sup> and in carefully controlled normal cases without the production of liver damage as measured by the Quick hippuric acid and bromsulfalein tests or by pterius index readings. Whereas clinical survival does not mean



that damage to vital organs has not been done, Cameron and de Saram<sup>27</sup> express an opinion based on experimental work that functional disturbance of the liver precedes actual damage which can be demonstrated by histologic methods. Sise<sup>168</sup> states his conviction concerning the effect of pentothal that "when the liver is well supplied with glycogen and when there is no lack of oxygen during and following anesthesia, liver damage need not be feared."

Marshall<sup>121</sup> mentions the administration of sulfanilamide as a contraindication to intravenous pentothal anesthesia. Adriani,<sup>8</sup> in investigations with rats to which sulfanilamide had been given, found that sub-anesthetic doses of pentothal became anesthetic, and that doses that were anesthetic to untreated animals were usually lethal to the sulfanilamized group. Lundy<sup>104</sup> reports that jaundice and general malaise have been observed clinically after the concurrent use of the two drugs. He and Adams<sup>5</sup> suggest that pentothal not be used within twenty-four or forty-eight hours after the administration of another sulfur-containing drug. Other writers<sup>105, 150</sup> have sounded the same warning. However, Nosworthy<sup>135</sup> and Smith<sup>172</sup> report the administration of pentothal to patients to whom sulfapyridine had been given in large doses without demonstrable ill effects.

Clinicopathologic observations, as reported by several authors,<sup>30, 64, 116, 150, 186</sup> have demonstrated no significant changes in blood sugar, nonprotein nitrogen, uric acid, creatinine, and the Quick hippuric acid tests following sodium pentothal anesthesia. Kidney function as indicated by urinalysis is not affected.<sup>116</sup> Mild variations in blood sugar levels have not been of sufficient degree to influence sodium pentothal's favored use as an anesthetic of choice in diabetes.<sup>102, 207</sup>

Experimental work to determine the minimal lethal dose of pentothal sodium in rabbits<sup>87</sup> and dogs<sup>64</sup> has proved this value to be approximately 35 mg. per kilogram of body weight, one-half of which amount gives satisfactory anesthesia. Other investigators<sup>69, 131</sup> using rats and cats have estimated the minimal lethal dose to be from 90 to 225 mg. per kilogram, and Gruhzit and his co-workers<sup>56</sup> have stated that the ratio of the maximal tolerated dose to the minimal anesthetic dose is 4.5:1 in rats and 3.8:1 in dogs. Given to rabbits in a single dose, 10 mg. per kilogram of the drug was found to be detoxified after ten minutes, 25 mg. per kilogram after thirty minutes.<sup>87</sup> The results demonstrate that so rapidly is the drug destroyed that the clinical use of the intermittent method allows one dose to be partly detoxified before the next is administered. This becomes especially evident when it is considered that induction of anesthesia is usually obtained by the administration of less than 3 mg. per kilogram of body weight and that subsequent doses are less than 1 mg. per kilogram of body weight. The total amount of pentothal used in an operation lasting one hour varies

between 13 and 26 mg. per kilogram. Thus theoretically there is a very safe relationship between the probable minimal lethal dose in man and the amount required for anesthesia. Carraway<sup>30</sup> has reported autopsies on twelve patients who died several days after operation, in none of whom was found any pathologic change which he attributed to the pentothal sodium anesthesia.

Since immediate death of experimental animals after overdosage has been demonstrated to be due to respiratory paralysis without the effect of any other pathologic process,<sup>80, 86</sup> it follows logically that the recommended antidotes for pentothal sodium are various respiratory stimulants such as eoramine, pierotoxin, alpha-lobeline, metrazol, oxygen, and carbon dioxide.<sup>9, 28, 30, 31, 41, 44, 64, 80, 82, 90, 94, 100, 107, 108, 116, 133, 151, 164, 188, 200, 201</sup> These in many instances have appeared to be specific in the treatment of overdosage. A note of caution in the indiscriminate use of eoramine and metrazol was sounded by Maloney,<sup>118</sup> who demonstrated that stimulating doses of eoramine and metrazol, administered to barbitalized rabbits, caused transitory arousal at certain dosage levels, with death from depression in others; in every instance eoramine or metrazol, when combined with barbital, increased the duration of narcosis over that of the controls. It would seem that these observations merit further investigation.

Pierotoxin is reported to be the most effective antidote for pentothal.<sup>151, 201</sup> However, with its use there is a dangerous depression of cortical activity which comes on just before the onset of convulsions.<sup>41, 201</sup> A report of the Council on Pharmacy and Chemistry of the American Medical Association<sup>152</sup> on the "Present Status of Pierotoxin in Poisoning by the Barbiturates" states that when the two drugs are given together, there is "a combined form of poisoning by pierotoxin and the barbiturate with a mixture of stimulation and depression, from which within a given range of doses the animal ultimately recovers." The report suggests that the use of pierotoxin is justifiable in cases which can be carefully studied.

#### CLINICAL CONSIDERATIONS

The introduction of two important improvements in the technique of administration of intravenous anesthetic drugs made it possible for pentothal sodium to become an effective agent for general anesthesia. The first of these innovations was the development of the intermittent method of administration in which the anesthetic solution is injected as the indication arises. This technique permits the maintenance of an even anesthesia, and because of the rapidity of the destruction of the drug, makes sodium pentothal anesthesia as controllable<sup>28, 30, 82, 85, 116, 118, 127, 133, 168, 191</sup> and its use as safe as that of any inhalation anesthetic. The second fundamental improvement

in the technique of administration was the wide adoption of the continuous administration of oxygen during anesthesia. It has been shown that the barbiturates as a class affect the respiration by decreasing its depth. For this reason, adequate oxygenation during a barbiturate anesthesia can be obtained only by employing a concentration of oxygen higher than that found normally in the atmosphere. The continuous administration of high concentrations of oxygen during intravenous pentothal sodium anesthesia permits adequate oxygenation to be maintained during phases of anesthesia productive of muscular relaxation sufficient for any operative procedure.

In perusing the literature, one is impressed with the diversity of opinions concerning the scope of the usefulness of pentothal sodium. Many clinicians advise its use only for short anesthetics and in operations not requiring marked muscular relaxation.<sup>2, 4, 28, 67, 92, 96, 107, 109, 147, 159, 188</sup> This group lists as contraindications such conditions as asthma and cardiac decompensation, contending that abdominal operations and other procedures requiring muscular relaxation are not feasible under pentothal sodium. Still others<sup>29, 30, 82, 137, 139, 180, 187, 191</sup> have doubted that there are any contraindications to its use and indeed list so-called contraindications as actual indications for intravenous sodium pentothal. During the last two years, anesthetists who were at first very cautious in the use of pentothal have found wider uses for the method. This has been especially evident at the Mayo Clinic where each annual report since 1934 has shown pentothal sodium to be used in a greater proportion of the anesthetics given at that institution.<sup>106-111, 113</sup>

If barbiturate narcosis is carried to a stage of surgical anesthesia, respiration, although it remains regular, is insufficient in depth to supply the body with sufficient oxygen; hence a comparative anoxemia indicated by a peculiar pallor and mild cyanosis results. However, with the continuous administration of oxygen, whether by intranasal catheter, by mask, or by intratracheal catheter, this relative anoxemia is entirely eliminated, and the patient maintains a healthy color throughout the anesthesia.\* The concomitant use of oxygen and pentothal sodium thus permits the maintenance of a depth of anesthesia allowing complete muscular relaxation<sup>29, 38, 116, 120, 121, 132, 180</sup> and makes intravenous pentothal more widely applicable in various surgical procedures. At the same time the quiet breathing is in itself a considerable advantage in that abdominal operations are complicated less by interruption from straining and forceful respiration than under almost any other form of anesthesia;<sup>29, 30, 137, 157</sup> this factor undoubtedly has considerable effect in increasing the speed of operation and in reducing the morbidity therefrom.

\*Although no reports of its use have been seen, it is a matter of speculation whether or not a mixture of helium and oxygen might not make the use of intravenous pentothal sodium entirely safe in anesthetizing young children who with their narrow air passages have been considered not suited for this method.

Pentothal sodium is compatible clinically with all other common anesthetic agents and may be used as a supplement to local, regional, or inhalation anesthetics. Organe and Broad<sup>137</sup> and later Lundy and his co-workers<sup>111</sup> have suggested a technique by which nitrous oxide and oxygen in a fixed proportion\* are used as a basal anesthetic, with the addition of intravenous pentothal sodium to secure any desired depth of anesthesia. This method furnishes an adequate oxygen supply, and the small doses of pentothal which are necessary make possible a shorter recovery period even after prolonged anesthesia. Lundy<sup>104</sup> reports that after induction by pentothal sodium, intratracheal intubation can be accomplished in one-third the usual time and that a much smaller amount of the inhalation anesthetic drug is then required. Guedel<sup>57</sup> states that pentothal and evipal, employed for the induction of anesthesia before the administration of cyclopropane, are effective in preventing cardiac arrhythmias, by virtue of their action in elevating the threshold of activity of the autonomic nervous system and the conductive mechanism of the heart.

Pentothal is finding increasing use as a supplement to spinal anesthesia<sup>7, 61, 77, 123, 160</sup> both to prolong the anesthesia, when the operative procedure consumes more than the expected time, and to cause unconsciousness in the patient undergoing a long operation under spinal anesthesia. Jarman,<sup>77</sup> who anesthetizes his patients with pentothal before administering the spinal anesthetic agent, believes that in this way he is able to reduce the incidence of backaches and headaches which frequently follow spinal anesthesia. Hand and Sise<sup>61</sup> state that it is their custom to administer intravenous pentothal to a patient undergoing an operation upon the stomach under impregnated spinal anesthesia as soon as the surgeon decides to perform a long procedure such as gastric resection. They point out that muscular relaxation usually outlasts sensory anesthesia and that pentothal in small amounts will give adequate relief from pain and mental stress under such circumstances. Adams and Lundy<sup>7</sup> suggest light pentothal narcosis as an effective remedy for nausea occurring during spinal anesthesia.

Aside from offering a considerable margin of safety and a wide utility, a good anesthetic should be acceptable to the patient. That this is true of pentothal sodium is adequately attested by the testimony of those to whom it has been administered. Organe and Broad,<sup>137</sup> in calling attention to the short postoperative phase of euphoria frequently experienced, tell of the English patient who described his experience as "better than a trip to Brighton." Phillips<sup>142</sup> reports that it is a common experience to find a patient eating a hearty lunch within two hours

\*Lundy uses 50 per cent nitrous oxide. Organe and Broad, 85 per cent nitrous oxide. While the latter authors report that the patient's color is good with the use of 15 per cent oxygen, this does not correspond with other experience, and such a low concentration of oxygen is not to be recommended.

following operation. Lahey,<sup>93</sup> in giving his personal experience as a patient, calls pentothal "a delightful anesthetic."

Induction is a matter of a few seconds after the injection is begun. There is no excitement during the second stage, the patient drifting into unconsciousness as if in normal sleep. This characteristic is of especial value in the management of the hypertensive and nephritic patient.<sup>105</sup> Taking advantage of the rapidity and quietness of induction, the surgeon is able to shorten the period of anesthesia by preparing the field of operation prior to the beginning of the anesthetic.<sup>29, 31</sup> Because of the similarity of the mode of induction to the universal "blood test,"<sup>29, 30, 85, 116, 123, 145, 159, 166</sup> the usually apprehensive thyrotoxic patient may be put to sleep in her room without any knowledge that operation is contemplated. Long, Mickal, and Ochsner<sup>97</sup> have shown that the wisdom of this method of induction is reflected in the lessening of postoperative reaction in the hyperthyroid patient as indicated by lowered pulse and temperature curves.

One of the most desirable characteristics of the recovery period following intravenous pentothal is the patient's freedom from nausea and vomiting.<sup>64</sup> Jarman and Abel<sup>80</sup> reported 1,000 cases without a single instance of vomiting where preliminary medication had not been used. Cameron<sup>28</sup> reported 225 cases in which the only instance of vomiting followed an opiate. In Rawlings' series of 400 cases,<sup>150</sup> there was not a single instance of postoperative vomiting or headache. Not all clinicians have had such perfect records, but the fact seems to be established that postoperative vomiting is greatly reduced, a factor which is of immense importance as regards the patient's comfort and welfare. The acidosis associated with postoperative vomiting is a severe handicap, particularly to the diabetic patient, and makes the selection of an anesthetic drug which does not cause nausea particularly desirable in this group of patients.<sup>140</sup> There is also an absence of excessive sweating during the operative and recovery periods,<sup>30, 38, 106</sup> a characteristic which must be partially responsible for the fact that shock seems to be less than after other types of anesthesia.<sup>96, 99, 104, 106, 116, 166</sup> Following short operations, the length of the recovery period is extremely short, being calculated by various writers<sup>2, 28, 107, 137</sup> as from five to thirty minutes. Its length is approximately proportionate to the amount of the drug administered. Following the longer procedures, full recovery may be delayed for as long as six to twelve hours.<sup>35, 137</sup> However, even in these cases, the patient may be roused in from ten to sixty minutes,<sup>29, 116</sup> although, undisturbed, he prefers to sleep on. Postoperative restlessness has been reported as a rare complication<sup>29, 49, 88, 121</sup> with an incidence in a large series of cases of 0.05 per cent. Davison and Rudder<sup>29</sup> report the occasional and unexplained occurrence of hyperpyrexia during the post-

operative period, with fever of from 102° to 103° F. lasting six to eight hours, but state that they have never seen a bad result from its occurrence.

Whereas intravenous sodium pentothal is employed by some surgeons as the anesthetic of choice in all surgical procedures,<sup>29, 30, 191</sup> its use is limited to certain operations by others. The absence of the anesthetist and his apparatus from the region of the operative field makes the use of intravenous pentothal desirable in operations upon the head and neck, particularly in those cases in which the use of the cautery or electrosurgical unit creates a distinct fire hazard. It is reported as a desirable anesthetic by urologists,<sup>136, 184, 186</sup> ophthalmologists,<sup>98</sup> psychiatrists and neurologists,<sup>14, 48, 51, 130, 134, 150</sup> bronchoscopists and laryngologists,<sup>6, 34, 121</sup> it is used to control the convulsions caused by local and general anesthetic agents, by tetanus and eclampsia<sup>73, 99, 102, 127, 159, 162</sup> and to create a phase of "twilight sleep" permitting more careful investigation and treatment of personality problems.<sup>13, 40, 67, 176\*</sup>

The elderly and the debilitated tolerate intravenous pentothal sodium especially well,<sup>2, 5, 64, 105, 148</sup> and it is reported as the method of choice not only in these poor risk groups but also in diabetes,<sup>7, 102, 207</sup> myocardial degeneration,<sup>15, 52</sup> asthma, chronic bronchitis, and pulmonary tuberculosis,<sup>82, 102, 137</sup> surgical shock,<sup>99, 106, 116</sup> and in patients in whom, for one reason or another, inhalation and spinal anesthetics are contraindicated.<sup>107, 116</sup> It is reported as the anesthetic of choice in manipulative surgery<sup>41, 120</sup> where the low incidence of vomiting makes it desirable in a group of patients who frequently have eaten recently.

Some of the most ardent exponents of pentothal are those men who have employed it in the field of obstetrics. Kassebohm and Schreiber<sup>52</sup> have reported 250 cases in which intravenous evipal or sodium pentothal was used during childbirth without the occurrence of alarming signs or symptoms in mother or child. They and other writers<sup>11, 66, 91, 157, 175, 177</sup> have recommended it as an analgesic agent during the final stages of labor and during cesarean section. They believe this form of anesthesia to be especially suited to obstetrical practice for several reasons: it has no effect upon uterine contractions except to enhance slightly their force, a factor which is thought to shorten labor, no depression of infant respiration has been noticed; no instance of post-partum hemorrhage influenced by the drug has been observed, a state of analgesia can be deepened quickly to one of anesthesia on occasion; patients under the effect of pentothal sodium were very amenable to suggestion and co-operation was easily obtained. This last characteristic was of great value in Horsley's<sup>66</sup> experience in the management of childbirth in a mental hospital. The series reported by Kassebohm and Schreiber<sup>52</sup> in-

\*It appears to be of little value as an adjunct to crime detection since subjects partially under its influence can be or tell the truth without memory of the experience.

cluded the successful management during labor of a case of status asthmaticus, one of a decompensated rheumatic heart, and a third of severe pyelitis.

Intravenous pentothal sodium is proving valuable to British anesthetists in the exigencies of military surgery.<sup>70, 79, 124</sup> It is of particular value to victims of chemical warfare when it is desirable to use an anesthetic agent which is not irritating to the lungs. Solutions are relatively stable for from twenty-four to forty-eight hours, and as much as 500 c.c. can be made up at once and used over that period. Because of the availability of the drug, the ease with which it is transported and administered, the short induction time and the quiet recovery, important time and energy can be conserved when one anesthetist must be responsible for numerous anesthetics in a short period.

#### METHOD OF ADMINISTRATION

The apparatus used for intravenous pentothal administration may be as simple as a sterile syringe and a small-bore intravenous needle. Various amplifications of these have consisted largely of apparatus for stabilizing the source of supply of the anesthetic solution. Some anesthetists employ a three-way valve which allows the continuous administration of intravenous fluids during operation with the addition of the pentothal sodium solution when indicated. Others have made use of various types of stands for holding the syringe containing the solution. It can be injected into the tubing through which normal saline solution or blood is being given intravenously, but it is said to form a precipitate when mixed with glucose solution.<sup>61</sup>

Preoperative sedation with a "heavy" barbiturate, an opiate, and atropine is considered generally to be desirable, although a few anesthetists prefer to use nothing besides atropine preoperatively in order to avoid undue depression during and following operation. Long, Miekal, and Ochsner<sup>97</sup> studied fifty patients undergoing thyroidectomy and demonstrated that postoperatively the elapsed time before recovery from the anesthetic was much shorter in those patients receiving little preoperative sedation and pentothal anesthesia supplemented by ethylene and cyclopropane than in those patients receiving a "heavy" barbiturate preoperatively and inhalation anesthesia alone. Atropine is thought to minimize excessive tracheobronchial secretions, and, by decreasing vagal tone, to act as a prophylactic agent against transitory hiccupping, sneezing, and laryngeal spasm which have been observed infrequently during the induction of the anesthesia.<sup>10, 70, 114, 126, 130, 163, 180, 188</sup> The occurrence of laryngeal spasm has been attributed to the presence of mucus in the larynx<sup>130</sup> and to an improper speed of injection of the anesthetic drug.<sup>114</sup> Adriani and Rouvenstein<sup>19</sup> in an experimental study showed that pentothal produces a constrictor effect upon the bronchial

musculature through the agency of parasympathetic stimulation, an effect which can be prevented by the prophylactic use of atropine sulfate.

The pentothal sodium is dissolved in sufficient distilled water to make the desired solution. Since it has been shown that the incidence of phlebitis in the vein receiving the solution is directly proportionate to the concentration of the drug<sup>104</sup> (1 case in 1,000 with the use of 5 per cent solution; 1 case in 3,000 with 2.5 per cent solution), a concentration of 5 or 2.5 per cent is usually employed for induction of anesthesia while a 2.5 or 1.25 per cent solution is used for subsequent injections.

No established dosage can be indicated because of the marked variation in individual susceptibility, but it has been stated that the necessary dosage varies directly as the muscular component of the patient.<sup>43</sup> The toxic or cachectic patient usually requires a proportionately smaller amount.<sup>64</sup> As a rule, from 4 to 8 c.c. of a 2.5 per cent solution is required for induction of anesthesia with the additional administration of 1 or 2 c.c. as the indications arise. A total dosage of 1 to 2 Gm. is usually sufficient to maintain adequate relaxation for an hour's anesthesia. The use of as much as 3.15 Gm. has been reported<sup>159</sup> during an anesthesia of five and one-fourth hours for a neurosurgical procedure. The depth of anesthesia is best judged by the degree of muscular relaxation which is present; anesthesia sufficient to produce abdominal relaxation likewise will cause complete relaxation of the muscles of mastication. Rivett and Quayle<sup>157</sup> stress the fact that even light anesthesia gives good muscular relaxation if the surgeon is not rough in handling these structures. The condition of the patient must be watched carefully by constant observation of the blood pressure, the rate and volume of the pulse, and the color of the mucous membranes and nail beds.<sup>145</sup> Since respiration may be all but imperceptible, Landy<sup>100</sup> has devised a cotton "butterfly" which he attaches to the patient's upper lip so that the movement of air through the nostrils may be visualized. Heard<sup>66</sup> states that a widely dilated pupil with a fixed eyeball means momentary overdosage, while a widely moving eye with a pupil of normal size and activity indicates returning consciousness. A desirable state of surgical anesthesia is indicated by a fixed or slowly moving eyeball with a moderately dilated pupil reacting sluggishly to light.

Maintenance of ready access to an adequate supply of oxygen is essential. For this purpose the anesthetist must devise a patent airway by holding forward the jaw or by employing mechanical aids if necessary. Oxygen should be administered throughout the anesthesia by nasal catheter, by one of the several types of masks or by an intratracheal tube. After the operation the patient must be attended constantly until his reflexes return. It is usually necessary to support the jaw during a part of this period. Landy<sup>100</sup> advises the continuous administration of oxygen until signs of recovery appear.



The addition of various respiratory stimulants to the anesthetic solution has been reported by several authors<sup>28, 100, 109, 188</sup> who have observed as much as 30 per cent increase in the respiratory rate with a concomitant increase in depth of respiration. Other anesthetists employ picrotoxin, coramine, or metrazol routinely at the end of the operative procedure. On the occasion of need for an antidote for pentothal sodium overdosage, one of these drugs may be given repeatedly intravenously in full therapeutic dosage.<sup>28, 34, 82, 151, 152, 188, 201</sup> The general tendency, however, is to abandon the routine use of these drugs.<sup>109</sup>

TABLE I  
INTRAVENOUS PENTOTHAL SODIUM ANESTHESIA

Australian Medical Congress	9	Moore	500
Berkwitz	600	Murphy	100
Bourne	116	Nicholson and Sise	177
Brown and Troup	56	O'Crowley and Chmelnik	250
Bullard	718	Organe and Broad	236
Cameron	225	Payne	1
Carraway	5,963	Phillips	500
Chaney	14	Piekenbrock and Olsen	78
Cook	1	Poole and Long	25
Cooper	27	Porter	100
Davies	9	Pratt, Tatum, Hathaway, and Water	45
Davison and Rudder	1,524	Rawlings	400
Dixon	18	Rivett and Quayle	42
Drury	16	Ruth, Tovell, Milligan, and Charleroy	5,500
Fisher	175	Schindler	1
Gardner, Nosik, and Brubaker	25	Selman	50
Garofalo	1,045	Shackleford	50
Gold and Garofalo	1	Sise and Ford	146
Haskell	20	Smith	30
Heard	60	Smith	106
Horsley	2,000	Solomons	43
Hotten	1,500	Somerfield and Tovell	1
Hunt and Lundy	25,001	Thomas	3,100
Hutchison, Mitchell, and McHugh	5	Tucker	377
Jarman	1,326	Vaizey	1
Kassebohm and Schreiber	125	Van der Post	300
Knight	150	Villar Andrade	118
LaBrecque	44	Wilcox and Tovell	19
Lahey	1	Williams	4
Long, Mickal, and Ochsner	25	Woodbridge	282
Long	250	Zierold	160
Lorhan, Westphal, Grandstaff	227		
Marshall	333		
Miller and Tovell	500	Total	54,851

#### STATISTICAL DATA

That intravenous pentothal sodium is gaining a deserved popularity is attested by series of figures such as those from the Mayo Clinic<sup>111</sup> which reports that in 1940 this method was employed alone or in combination in 30.5 per cent of all instances in which an anesthetic was administered. A complete review of all the American and British literature has been made and a series of 54,851 anesthetics by intravenous pentothal sodium has been collected (Table I). Twelve deaths are re-

ported to have occurred during anesthesia, two afterward. A brief analysis of these is necessary to formulate a mortality rate.

1. Organe and Broad<sup>137</sup> report a death in a man, 88 years of age, whose abdomen was opened because of a ruptured peptic ulcer; this death, they state, was not due to the anesthesia.

2. Cameron<sup>25</sup> describes an obese diabetic patient who succumbed twenty-five minutes after the induction of anesthesia; the autopsy showed multiple cardiac infarcts.

3. Carraway<sup>30</sup> reports 3 deaths in his series: an elderly patient with a strangulated hernia who vomited and aspirated into the lungs large quantities of fluid during the second stage of anesthesia.

4. A negro male with a crushed hand whose death was proved at autopsy to be due to air emboli.

5. A hypertensive patient with an enormous heart who ill-advisedly was given an anesthetic and who died in the second stage of anesthesia.

6. One of Cooper's<sup>34</sup> patients died from massive pulmonary hemorrhage during bronchoscopy in a case of lung abscess.

7. Wileox and Tovell<sup>203</sup> report the death of a diabetic patient following an operation in which intravenous pentothal sodium anesthesia was employed; however, they fail to state the length of elapsed time or whether the death was influenced by the anesthetic. It is interesting to note that the mortality in the group receiving pentothal sodium intravenously was 5.3 per cent while the mortality rate in their entire series of 236 operations on diabetic patients was 12.2 per cent.

8. Davison and Rudder<sup>25</sup> report "one death in which anesthesia played a part," that of a young negro with bilateral pulmonary tuberculosis who had a local anesthetic supplemented by pentothal. Four hours after operation there was a respiratory collapse and death.

9, 10, 11, 12. Jarman<sup>75</sup> reports 4 deaths at General Hospital during 1938 in patients, each of whom had received pentothal sodium in combination with several other anesthetic agents.

13. Patterson<sup>140</sup> reports 2 deaths during pentothal anesthesia. One occurred in a woman, 56 years of age, who had a long history of cardiac insufficiency and was classified as a poor risk. After she was given 5 c.c. of a 2.5 per cent solution of pentothal sodium for the extraction of a tooth, her whole body became rigid. Although her heart continued to beat for three minutes, artificial respiration was not effective because of the fixation of the patient's thorax in expiration. No mention is made of the availability of oxygen or of adequate apparatus for its administration.

14. A male patient acutely ill from Ludwig's angina was given 5 c.c. of a 5 per cent solution of pentothal sodium and the operation was begun and one-half minute later...

to have respiratory difficulty and ceased to breathe, although his heart continued to beat for five minutes. This episode is similar to those reported by Weese<sup>198</sup> in which deaths from respiratory paralysis occurred during operations for sublingual infections in patients incompletely anesthetized with evipal.

Eliminating the cases reported by Organe and Broad, Cooper, Wilcox and Tovell, and Jarman, there remain 7 instances in which death may be ascribed to the anesthetic agent; 4 of these might have been avoided had proper facilities been available or had better preparation of the patient and better clinical judgment been used. Remarkable in this collection of 54,851 cases is the absence of any single report of post-operative pulmonary collapse or pneumonia; symptoms of milder respiratory complications were almost as rare.

Although an honest effort has been made in the preparation of these figures to avoid duplication and other inaccuracies, we do not presume that they represent an accurate estimation of the actual use of pentothal sodium. Numerous clinicians have not reported their experiences and others have done so without enumerating their patients or mentioning anesthetic mortality. Up until May, 1940, the manufacturers had distributed more than 1,800,000 ampoules in this country and in England,<sup>1</sup> but how much of this remains still in the hands of wholesalers and branches is not known. Likewise, the accuracy of the mortality rate which we have tried to establish undoubtedly will not stand the test of larger series, but will serve for the present to point the risk which this method entails.

As in the use of all other types of anesthesia, the greatest danger to the patient lies in the administration of intravenous pentothal by inexperienced anesthetists. This point is made poignantly again by Jarman<sup>79</sup> who, in collecting the 1,300 anesthetic deaths reported between 1921 and 1939, found that 80 per cent of the fatalities occurred with house officers in charge, whereas only 8 per cent of the reported deaths were among patients managed by full-time anesthetists. Lahey,<sup>93</sup> Lundy and Tovell,<sup>106</sup> and Ruth, Tovell, Milligan, and Charleroy<sup>150</sup> reiterate this warning for those who would use intravenous pentothal sodium. However, numerous writers, among whom are Jarman and Abel,<sup>80</sup> Kassebohm and Schreiber,<sup>82</sup> Lundy and his associates,<sup>113</sup> Mallinson,<sup>116</sup> Murphy,<sup>172</sup> and Thomas,<sup>150</sup> attest the safety of this agent when used by a cautious and skilled anesthetist who has at hand adequate equipment.

#### REFERENCES

1. Abbott Laboratories: Personal communication.
2. Adams, R. C.: *The Present Status of Intravenous Administration of Pentothal Sodium in Institutional and Private Practice*, *Canad. M. A. J.* 38: 330, 1938.
3. Adams, R. C.: *Discussion of Delmonico*,<sup>79</sup>
4. Adams, R. C.: *Intravenous Anesthesia*, *Surg., Gynec. & Obst.* 68: 719, 1939.

5. Adams, R. C.: Intravenous Anesthesia, *J. Iowa M. Soc.* 30: 148, 1940.
6. Adams, R. C.: Recent Advances in Anesthesia, *Arch. Surg.* 40: 364, 1940.
7. Adams, R. C., and Lundy, J. S.: Factors Influencing the Choice of the Anesthetic Agent and Some Suggestions of Anesthetic Technic, *S. Clin. North America* 20: 915, 1940.
8. Adriani, John: Effect of Anesthetic Drugs Upon Rats Treated With Sulphanilamide, *J. Lab. & Clin. Med.* 24: 1066, 1939.
9. Adriani, John: The Fate of Anesthetic Drugs in the Body, *Anesthesiology* 1: 312, 1940.
10. Adriani, John, and Rovenstine, E. A.: Autonomic Responses of Bronchial Tissue to Various Anesthetic Drugs, *Am. J. Physiol.* 133: 192, 1941.
11. Allen, E. V., Lundy, J. S., and Adson, A. W.: Preoperative Prediction of Effects on Blood Pressure of Neurosurgical Treatment of Hypertension. *Proc. Staff Meet., Mayo Clin.* 11: 401, 1936.
12. Australian Medical Congress: Discussion on Deaths of Patients Under Anesthesia, *M. J. Australia* 1: 995, 1938.
13. Berkwitz, N.: Faradic Shock Treatment of the "Functional" Psychoses, *Journal-Lancet* 59: 351, 1939; *Dig. Treat.* 3: 515, 1940.
14. Berkwitz, N.: Faradic Shock in Treatment of Functional Mental Disorders, *Arch. Neurol. & Psychiat.* 44: 760, 1940.
15. Betlach, C. J.: Effects of Pentothal Sodium on the EKG of Patients With Essential Hypertension, *Proc. Staff Meet., Mayo Clin.* 13: 199, 1938.
16. Blackberg, S. N., and Hrubetz, Caroline: Factors Influencing Pentothal Anesthesia, *J. Lab. & Clin. Med.* 22: 1224, 1937.
17. Bourne, Wesley: Analgesia and Anesthesia in Obstetrics: Pentothal Sodium, Cyclopropane and Vinyl Ether, *Brit. J. Anesth.* 15: 1, 1937.
18. Bourne, Wesley: Analgesia and Anesthesia in Obstetrics, *New York State J. Med.* 37: 1905, 1937.
19. Bourne, Wesley, and Pauly, A. J.: Thiobarbiturates in Obstetrics: Pentothal and Thioethamyl, *Canad. M. A. J.* 40: 437, 1939.
20. Brown, Gilbert, and Troup, Gilbert: Experiences With "Pentothal Sodium," *M. J. Australia* 1: 989, 1938.
21. Bullard, O. K.: Intravenous Anesthesia in Office Practice for Operations in Exodontia and Oral Surgery: Based on an Experience of 946 Cases, *Anesth. & Analg.* 19: 26, 1940.
22. Burstein, C. L., and Rovenstine, E. A.: Respiratory Para-sympathetic Action of Some Shorter Acting Barbituric Acid Derivatives, *J. Pharmacol. & Exper. Therap.* 63: 42, 1938.
23. Burstein, C. L.: Effect of Some Short Acting Barbituric Acid Derivatives on Intestinal Activity in Vivo, *Proc. Soc. Exper. Biol. & Med.* 40: 122, 1939.
24. Bush, M. T., and Butler, T. C.: The Metabolic Fate of N Substituted Derivatives of Barbitol, *J. Pharmacol. & Exper. Therap.* 68: 278, 1940.
25. Butler, T. C., and Bush, M. T.: The Metabolic Fate of N Methyl Barbituric Acids, *J. Pharmacol. & Exper. Therap.* 65: 295, 1939.
26. Cady, J. B., Horton, B. T., and Adson, A. W.: Drop in Blood Pressure Produced by Sodium Amytal, Sodium Nitrite, Amyl Nitrite, and Pentothal Sodium: Comparative Study, *Proc. Staff Meet., Mayo Clin.* 11: 825, 1936.
27. Cameron, G. R., and de Saram, G. S. W.: The Effect of Liver Damage on the Action of Some Barbiturates, *J. Path. & Bact.* 48: 49, 1939.
28. Cameron, W. A.: Pentothal Sodium as an Intravenous Anesthetic, *Anesth. & Analg.* 16: 230, 1937.
29. Carraway, B. M., and Carraway, C. N.: Intravenous Anesthesia; a Clinical Study of 1900 Cases, *Am. J. Surg.* 39: 776, 1938.
30. Carraway, C. N.: Pentothal Sodium Oxygen Anesthesia in Major Surgery, *South. Surgeon* 9: 313, 1940.
31. Challis, J. H. T.: Basal Anesthesia for Short Operations, *Brit. M. J.* 2: 386, 1937.
32. Chaney, R. H.: Discussion of Davison and Rudder.<sup>28</sup>
33. Cook, W. B.: Convulsions Associated With Nitrous Oxide Ether Anesthesia, *Northwest. Med.* 39: 182, 1940.
34. Cooper, M. P.: The Use of Pentothal Sodium Intravenously for Anesthesia in Laryngoscopy, Bronchoscopy, and Esophagoscopy, *Anesth. & Analg.* 18: 181, 1939.

to have respiratory difficulty and ceased to breath, although his heart continued to beat for five minutes. This episode is similar to those reported by Weese<sup>108</sup> in which deaths from respiratory paralysis occurred during operations for sublingual infections in patients incompletely anesthetized with evipal.

Eliminating the cases reported by Organe and Broad, Cooper, Wilcox and Tovell, and Jarman, there remain 7 instances in which death may be ascribed to the anesthetic agent; 4 of these might have been avoided had proper facilities been available or had better preparation of the patient and better clinical judgment been used. Remarkable in this collection of 54,851 cases is the absence of any single report of post-operative pulmonary collapse or pneumonia; symptoms of milder respiratory complications were almost as rare.

Although an honest effort has been made in the preparation of these figures to avoid duplication and other inaccuracies, we do not presume that they represent an accurate estimation of the actual use of pentothal sodium. Numerous clinicians have not reported their experiences and others have done so without enumerating their patients or mentioning anesthetic mortality. Up until May, 1940, the manufacturers had distributed more than 1,800,000 ampoules in this country and in England,<sup>1</sup> but how much of this remains still in the hands of wholesalers and branches is not known. Likewise, the accuracy of the mortality rate which we have tried to establish undoubtedly will not stand the test of larger series, but will serve for the present to point the risk which this method entails.

As in the use of all other types of anesthesia, the greatest danger to the patient lies in the administration of intravenous pentothal by inexperienced anesthetists. This point is made poignantly again by Jarman<sup>78</sup> who, in collecting the 1,300 anesthetic deaths reported between 1921 and 1939, found that 80 per cent of the fatalities occurred with house officers in charge, whereas only 8 per cent of the reported deaths were among patients managed by full-time anesthetists. Lahey,<sup>93</sup> Lundy and Tovell,<sup>106</sup> and Ruth, Tovell, Milligan, and Charleroy<sup>110</sup> reiterate this warning for those who would use intravenous pentothal sodium. However, numerous writers, among whom are Jarman and Abel,<sup>80</sup> Kassebohm and Schreiber,<sup>82</sup> Lundy and his associates,<sup>113</sup> Mallinson,<sup>116</sup> Murphy,<sup>112</sup> and Thomas,<sup>180</sup> attest the safety of this agent when used by a cautious and skilled anesthetist who has at hand adequate equipment.

#### REFERENCES

1. Abbott Laboratories: *Personal communication.*
2. Adams, R. C.: The Present Status of Intravenous Administration of Pentothal Sodium in Institutional and Private Practice, *Canad. M. A. J.* 38: 330, 1938.
3. Adams, R. C.: Discussion of Delmonico,<sup>79</sup>
4. Adams, R. C.: Intravenous Anesthesia, *Surg., Gynec. & Obst.* 68: 719, 1939.

64. Heard, K. M.: Pentothal: A New Intravenous Anesthetic, *Canad. M. A. J.* 34: 628, 1936.
65. Herb, I. C.: From Dean Lewis: Practice of Surgery, Hagerstown, Md., 1940, W. F. Prior Co., vol. I, chap. 3, pp. 40.
66. Horsley, Stephen: Intravenous Anesthesia for Childbirth in a Mental Hospital, *Lancet* 1: 690, 1936.
67. Horsley, J. S.: Pentothal Sodium in Mental Hospital Practice, *Brit. M. J.* 1: 938, 1936.
68. Horsley, J. S.: The Intracranial Pressure During Barbitol Narcosis, *Lancet* 1: 141, 1937.
69. Horsley, J. S.: Pentothal Acid: a New Basal Anesthetic, *Brit. J. Anesth.* 16: 1, 1938.
70. Hotten, W. I. T.: Anesthesia in Relation to War Conditions, *M. J. Australia* 1: 132, 1940.
71. Hrubetz, M. C., and Blackberg, S. N.: The Influence of Nembutal, Pentothal, Seconal, Amytal, Phenobarbital, and Chloroform on Blood Sugar Concentration and Carbohydrate Mobilization, *Am. J. Physiol.* 122: 759, 1938.
72. Hubbell, A. O., and Adams, R. C.: Intravenous Anesthesia for Dental Surgery With Sodium Ethyl (1-Methylbutyl) Thiobarbituric Acid, *J. Am. Dent. A.* 27: 1186, 1940.
73. Hunt, A. B., and Lundy, J. S.: Combined Local and Intravenous Anesthesia for Caesarean Section, *Proc. Staff Meet., Mayo Clin.* 16: 191, 1941.
74. Hutchison, Keith, Mitchell, H. S., and McHugh, Holley: Tonsillectomy Under Intravenous Anesthesia in Children Suffering From Chronic Respiratory Diseases, *Canad. M. A. J.* 39: 237, 1938.
75. Hutton, John H., and Tovell, R. M.: Pentothal Sodium for Intravenous Anesthesia, *Surg., Gynec. & Obst.* 64: 888, 1937.
76. Jackman, R. J.: Preoperative and Postoperative Care in Anorectal Surgery, *S. Clin. North America* 20: 1077, 1940.
77. Jarman, Ronald: The Combination of Intravenous With Spinal Anesthesia, Using Pentothal and Percaine, *Brit. J. Anesth.* 15: 20, 1937.
78. Jarman, Ronald: Deaths Under Anesthesia, From 1921 to Present Date, *Brit. J. Anesth.* 16: 100, 1939.
79. Jarman, Ronald: Anesthesia in Wartime, *Brit. M. J.* 1: 896, 1939.
80. Jarman, Ronald, and Abel, A. L.: Intravenous Anesthesia With Pentothal Sodium, *Lancet* 1: 422, 1936.
81. Jarman, Ronald, and Abel, A. L.: Technique of Intravenous Anesthesia, *Lancet* 1: 600, 1936.
82. Kassebohm, F. A., and Schreiber, M. J.: Intravenous Anesthesia in Obstetrics, a Comparative Study of Pentothal and Evipal Soluble With a Report of 250 Cases, *Am. J. Surg.* 40: 377, 1938.
83. Knight, Ralph: Discussion of Ruth et al.<sup>159</sup>
84. Knight, R. T.: Practical Points in Anesthesia, *Minnesota Med.* 22: 105, 1939.
85. Kohn, Richard: Studies on the Barbiturates With Reference to Individual Susceptibility, *Anesth. & Analg.* 17: 218, 1938.
86. Kohn, Richard, and Lederer, Ludwig: Pentothal Studies With Special Reference to the Electrocardiogram, *J. Lab. & Clin. Med.* 23: 717, 1938.
87. Kohn Richards, R., and Grimes, Clyde: Detoxification of Barbiturates and the Influence of the Method of Administration: Demonstrated With Nembutal and Pentothal, *Anesth. & Analg.* 18: 139, 1939.
88. Kohn Richards, R., and Grimes, Clyde: Effect of Certain Barbiturates on the Response to Vasoactive Substances, *Anesth. & Analg.* 19: 31, 1940.
89. Kozelka, F. L., and Hine, C. H.: Study of the Cumulative Effect of the Thiobarbituric Acid Derivatives, *J. Pharmacol. & Exper. Therap.* 66: 20, 1939.
90. Krop, Stephen, and Hazleton, L. W., and Koppanyi, Theodore: Studies on Barbiturates. XXIII: The Effects of Analeptics on Depression by Pentobarbital Used in Experimental Cocaine Poisoning, *Anesth. & Analg.* 20: 15, 1941.
91. LaBreeque, F. C.: Intravenous Anesthesia in Obstetrics, *New England J. Med.* 219: 954, 1938.
92. Lahey, F. H.: Modern Development in Anesthesia and Anesthetists, *South. M. J.* 31: 29, 1938.
93. Lahey, F. H.: Discussion of Davison and Rudder.<sup>18</sup>

35. Dabbs, R. T.: Pentothal Sodium as an Intravenous Anesthetic, *Mississippi Doctor* 16: 19, 1939.
36. Davies, R. M.: Case of Repeated Administration of Pentothal Sodium, *Brit. M. J.* 2: 450, 1940.
37. Davison, T. C., and Rudder, F. F.: A Mechanical Device for the Administration of Intravenous Anesthetics, *Am. J. Surg.* 50: 323, 1940.
38. Davison, T. C., and Rudder, F. F.: The Use of Pentothal Sodium-Oxygen Anesthesia as a Total Anesthetic Agent in Major Surgical Procedures, *J. M. A. Georgia* 29: 475, 1940.
39. Delmonico, E. J.: Tests for Derivatives of Barbituric Acid, *Proc. Staff Meet., Mayo Clin.* 14: 109, 1939.
40. Dicks, H., and Stungo, E.: Hypnotics in Psychotherapy, *Brit. M. J.* 1: 865, 1940.
41. Dille, James M., and Hazleton, L. W.: The Depressant Action of Pierotoxin and Metrazol, *J. Pharmacol. & Exper. Therap.* 66: 276, 1939.
42. Dixon, C. P.: Some Observations on Pentothal Sodium, *Brit. J. Anesth.* 15: 60, 1938.
43. Drury, G.: Intravenous Anesthesia, With Special Reference to Pentothal Sodium in Africans, *East African M. J.* 15: 256, 1938.
44. Duff, D. M., and Dille, J. M.: Distribution and Rate of Elimination of Pierotoxin, *J. Pharmacol. & Exper. Therap.* 67: 353, 1939.
45. Evans, Frankis: Thrombosis After Injection of Pentothal Sodium, *Lancet* 2: 252, 1939.
46. Fisher, Katherine: Pentothal Sodium Anesthesia as Used in a Small Hospital, *Kentucky M. J.* 39: 145, 1941.
47. Fulton, J. R.: Intravenous Anesthesia, *U. S. Naval M. Bull.* 38: 502, 1940.
48. Gardner, W. J., Nosik, W. A., and Brubaker, R. E.: Pentothal Sodium Anesthesia in Pneumo-Encephalography, *Cleveland Clin. Quart.* 7: 174, 1940.
49. Garofalo, Mario: The Present Status of Pentothal Sodium as an Anesthetic Agent, *J. Connecticut M. Soc.* 2: 550, 1938.
50. Gillman, S. W.: Pierotoxin in the Treatment of Collapse Due to Barbiturates, *Lancet* 1: 598, 1940.
51. Gold, L. H., and Garofalo, M. L.: Treatment of Aphonia With Intravenous Pentothal, *Anesthesiology* 1: 94, 1940.
52. Gruber, C. M.: On Certain Pharmacologic Actions of the Newer Barbituric Acid Compounds, *Am. J. Obst. & Gynec.* 33: 729, 1937.
53. Gruber, C. M.: The Effects of Anesthetic Doses of Sodium Thio-Pentobarbital, Sodium Thio-Ethamyl and Pentothal Sodium Upon the Respiratory System, the Heart and Blood Pressure in Experimental Animals, *J. Pharmacol. & Exper. Therap.* 60: 143, 1937.
54. Gruber, C. M., and Gruber, C. M., Jr., and Colosi, N. A.: The Irritability of the Cardiac Vagus Nerves as Influenced by the Intravenous Injections of Barbiturates, Thio-Barbiturates and Pierotoxin, *J. Pharmacol. & Exper. Therap.* 63: 215, 1938.
55. Gruber, C. M., Haury, V. G., and Gruber, C. M., Jr.: The Cardiac Arrhythmia, Characteristic Effect of the Thio-Barbiturates, as Influenced by Changes in Arterial Blood Pressure, *J. Pharmacol. & Exper. Therap.* 63: 193, 1938.
56. Gruhitz, O. M., Dox, A. W., Rowe, L. W., and Dodd, M. C.: A Pharmacologic Study of Certain Thiobarbiturates, *J. Pharmacol. & Exper. Therap.* 60: 125, 1937.
57. Guedel, A. E.: Cyclopropane Anesthesia, *Anesthesiology* 1: 13, 1940.
58. Gwathmey, J. T.: *Anesthesia*, ed. 2, New York, 1924, The Macmillan Co.
59. Hafkesbring, R., Greisheimer, E., and Magalhaes, H.: Effects of Repeated Anesthetic Doses of Barbiturates, *J. Pharmacol. & Exper. Therap.* 66: 95, 1939.
60. Hale, D. E.: Intravenous Anesthesia, *Proc. Staff Meet., Mayo Clin.* 10: 743, 1935.
61. Hand, L. V., and Sise, L. F.: Intravenous Agents as Supplementary Anesthetics, *Lahey Clinic Bull.* 13: 18, 1939.
62. Haskell, Benjamin: Intravenous Anesthetic Agents in Proctology, *Tr. Am. Proct. Soc.* 38: 144, 1937.
63. Hewer, C. L.: *Recent Advances in Anesthesia and Analgesia*, London, 1937, J. and A. Churchill, Ltd.

120. Marcus, P. S.: Pentothal: Anesthetic Agent of Choice for Reduction of Simple Fractures, *New England J. Med.* 222: 137, 1940.
121. Marshall, S. V.: Pentothal Sodium; a Review With an Analysis of 333 Cases, *M. J. Australia* 1: 382, 1939.
122. McClure, R. D., Hartman, F. W., Schnedorf, J. G., and Schelling, Victor: Anoxia; a Source of Possible Complications in Surgical Anesthesia, *Ann. Surg.* 110: 835, 1939.
123. Miller, L. J., and Tovell, R. M.: Pentothal Sodium, Its Field of Usefulness, *J. Maine M. A.* 31: 298, 1940.
124. Moore, R. H.: Anesthesia in Wartime, *Brit. M. J.* 2: 336, 1940.
125. Moore, R. H.: Dosage of Barbiturate Anesthetics, *Brit. M. J.* 2: 472, 1940.
126. Moore, R. H.: Continuous Pentothal Anesthesia, *Brit. M. J.* 1: 462, 1941.
127. Mousel, L. H.: An Unusual Case of Convulsions Under Anesthesia, *Proc. Staff Meet., Mayo Clin.* 15: 33, 1940.
128. Mousel, L. H.: Modern Trends in Anesthesia, *J. Kansas M. Soc.* 41: 279, 1940.
129. Mousel, L. H., and Lundy, J. S.: The Role of the Liver and the Kidneys From the Standpoint of the Anesthetist, *Anesthesiology* 1: 40, 1940.
130. Mousel, L. H., and Lundy, J. S.: Preoperative and Postoperative Sedation for Various Operations, *S. Clin. North America* 20: 907, 1940.
131. Mulinos, M. G.: Anesthetic Properties of Sodium-Ethyl-Pentyl, Malonyl-thiourea, *Proc. Soc. Exper. Biol. & Med.* 34: 506, 1936.
132. Murphy, O. J.: Pentothal Sodium Anesthesia, *Brit. M. J.* 2: 1308, 1936.
133. Myerson, Abraham: The Reciprocal Pharmacologic Effects of Amphetamine (Benzedrine) Sulphate and the Barbiturates, *New England J. Med.* 221: 561, 1939.
134. Nicholson, M. J., and Sise, L. F.: Pentothal Sodium Anesthesia for Encephalography, *New England J. Med.* 222: 994, 1940.
135. Nosworthy, M. D.: Report of Societies: Section on Surgery of the Royal Society of Medicine "Chest Injuries," *Brit. M. J.* 2: 842, 1940.
136. O'Crowley, C. R., and Chmelnik, A. G.: Pentothal Sodium Intravenous Anesthesia in Urology, *J. Urol.* 41: 649, 1939.
137. Organe, Geoffrey, and Broad, R. J. B.: Pentothal With Nitrous Oxide and Oxygen, *Lancet* 2: 1170, 1938.
138. Palmer, E. P.: Pentothal Sodium; a Basic Intravenous Anesthetic, *Southwest. Med.* 21: 316, 1937.
139. Palmer, E. P.: Basic Intravenous Anesthesia With Sodium Ethyl Thiobarbiturate, *South. M. J.* 32: 290, 1939.
140. Patterson, R. L.: Case Reports of Fatalities Following Intravenous Anesthesia, *Anesth. & Analg.* 20: 225, 1941.
141. Payne, R. T.: Extensive Thrombosis After Pentothal Sodium Injection, *Lancet* 1: 816, 1939.
142. Phillips, R. B.: Intravenous Anesthesia and How to Use It, *Mil. Surgeon* 87: 301, 1940.
143. Phillips, R. B.: Intravenous Anesthesia in Minor Surgery, *Am. J. Surg.* 50: 491, 1940.
144. Pickenbrock, F. J., and Olsen, P. F.: Intravenous Anesthesia and Its Uses, *J. Iowa M. Soc.* 30: 240, 1940.
145. Poole, W. L., and Long, C. H.: Report of the Use of Pentothal Sodium as an Intravenous Anesthetic, *J. Tennessee M. A.* 34: 340, 1941.
146. Porter, A. R.: Intravenous Anesthesia, Report of 100 Cases, *Memphis M. J.* 15: 3, 1940.
147. Pratt, T. W., Tatum, A. L., Hathaway, H. R., and Water, R. M.: Sodium Lithol (1 Methyl Butyl) Thiobarbiturate, *Am. J. Surg.* 31: 464, 1936.
148. Priestley, J. T., and Schulte, T. L.: Preoperative and Postoperative Care for Patients Who Have Operations of the Kidney, *S. Clin. North America* 20: 1049, 1940.
149. Ravdin, I. S.: Some Recent Advances in Surgical Therapeutics, *Ann. Surg.* 109: 321, 1939.
150. Rawlings, G. R.: Intravenous Anesthesia With Pentothal Sodium, *Indian M. Gaz.* 74: 722, 1939.
151. Reifstein, E. C., Jr., Reifstein, E. C., Sr., Mignault, J. W., and Raffaele, A. J.: PicROTOXIN in the Treatment of Acute Barbiturate Poisoning, *Ann. Int. Med.* 13: 1013, 1939.



94. Levi, A. A., and Krinsky, C. M.: The Effect of Coramine on Postpartum Patients Under the Analgesic Influence of Some Barbituric Acid Drugs, *New England J. Med.* 214: 362, 1936.
95. Lewis, A. E.: Intravenous Pentothal Sodium Anesthesia, *Northwest Med.* 37: 206, 1938.
96. Long, A.: Pentothal Sodium Anesthesia, *J. Roy. Nav. M. Serv.* 24: 66, 1938.
97. Long, Carroll H., Mickal, Abe, and Ochsner, Alton: The Use of Pentothal Sodium for the Induction of Anesthesia in Thyrotoxicosis, *Am. J. Surg.* In press.
98. Lorhan, P. H., Westphal, Corinne, and Grandstaff, Eleanor: Pentothal Sodium in Eye Surgery, *J. Kansas M. Soc.* 40: 193, 1939.
99. Lundy, J. S.: Intravenous Anesthesia: Preliminary Report of the Use of Two New Thiobarbiturates, *Proc. Staff Meet., Mayo Clin.* 10: 536, 1935.
100. Lundy, J. S.: A Method of Minimizing Respiratory Depression When Using Soluble Barbiturates Intravenously, *Proc. Staff Meet., Mayo Clin.* 10: 791, 1935.
101. Lundy, J. S.: Various Anesthetic Agents, Especially Some Newer Preparations, *Illinois M. J.* 70: 134, 1936.
102. Lundy, J. S.: Intravenous Anesthesia, *Am. J. Surg.* 34: 559, 1936.
103. Lundy, J. S.: Suggestions to Facilitate Venipuncture, *Proc. Staff Meet., Mayo Clin.* 12: 122, 1937.
104. Lundy, John S.: Intravenous and Regional Anesthesia, *Ann. Surg.* 110: 878, 1939.
105. Lundy, J. S., and Adams, R. C.: Intravenous Anesthesia, *Anesthesiology* 1: 145, 1940.
106. Lundy, J. S., and Tovell, R. M.: Annual Report for 1934 of the Section on Anesthesia; Including Data on Blood Transfusion, *Proc. Staff Meet., Mayo Clin.* 10: 257, 1935.
107. Lundy, J. S., Tovell, R. M., and Tuohy, E. B.: Annual Report for 1935 of Section on Anesthesia; Including Data on Blood Transfusion, *Proc. Staff Meet., Mayo Clin.* 11: 421, 1936.
108. Lundy, J. S., Tuohy, E. B., and Adams, R. C.: Annual Report for 1936 of Section on Anesthesia; Including Data on Blood Transfusion, *Proc. Staff Meet., Mayo Clin.* 12: 225, 1937.
109. Lundy, J. S., Tuohy, E. B., and Adams, R. C.: Annual Report for 1937 of the Section on Anesthesia; Including Data on Blood Transfusion, *Proc. Staff Meet., Mayo Clin.* 13: 177, 1938.
110. Lundy, J. S., Tuohy, E. B., Adams, R. C., and Mousel, L. H.: Annual Report for 1938 of the Section on Anesthesia; Including Data on Blood Transfusion, *Proc. Staff Meet., Mayo Clin.* 14: 273, 1939.
111. Lundy, J. S., Tuohy, E. B., Adams, R. C., Mousel, L. H., and Seldon, T. H.: Annual Report for 1939 of the Section on Anesthesia; Including Data on Blood Transfusion and a Review of Anesthetic Agents From 1921 to 1939, Inclusive, *Proc. Staff Meet., Mayo Clin.* 15: 241, 1940.
112. Lundy, J. S., Tuohy, E. B., Adams, R. C., and Mousel, L. H.: Clinical Use of Local and Intravenous Anesthetic Agents, *Proc. Staff Meet., Mayo Clin.* 16: 78, 1941.
113. Lundy, J. S., Tuohy, E. B., Adams, R. C., Mousel, L. H., and Seldon, T. H.: Annual Report for 1940 of the Section on Anesthesia; Including Data on Blood Transfusion and Graduate Training, *Proc. Staff Meet., Mayo Clin.* 16: 241, 1941.
114. Macintosh, R. R., and Pask, E. A.: Apparatus for Giving Intravenous Anesthetics Continuously, *Lancet* 2: 650, 1910.
115. MacPhail, F. L., Gray, H. R. D., and Bourne, Wesley: Pentothal Sodium as a Hypnotic in Obstetrics, *Canad. M. A. J.* 37: 471, 1937.
116. Mallinson, F. B.: Pentothal Sodium in Intravenous Anesthesia, *Lancet* 2: 1070, 1937.
117. Mallinson, F. B.: Management of Respiratory Depression During Anesthesia, *Brit. M. J.* 1: 123, 1940.
118. Maloney, A. H.: Contradictory Actions of Caffeine, Coramine, and Metrazol, *Quart. J. Exper. Physiol.* 25: 155, 1935.
119. Maloney, A. H.: The Short Acting Barbiturates as Intravenous Anesthetics, *Clin. Med. & Surg.* 45: 153, 1938.

185. Tovell, R. M., and Hinds, C. B.: Abdominal Block With General Anesthesia for Upper Abdominal Surgery, *J. A. M. A.* 115: 1690, 1940.
186. Tovell, R. M., and Thompson, G. J.: Pentothal Sodium Anesthesia in Urologic Practice, *J. Urol.* 36: 81, 1936.
187. Tucker, A. O.: Intravenous Anesthesia With Pentothal Sodium in General Surgery, *Northwest Med.* 38: 246, 1939.
188. Tuohy, E. B.: Intravenous Anesthesia With Pentothal Sodium, *Anesth. & Analg.* 16: 164, 1937.
189. Vaizey, J. M.: Toxic Jaundice Following Administration of Pentothal, *Brit. J. Anesth.* 15: 55, 1938.
190. Van der Post, C. W. H.: Pentothal Sodium in Anesthetics, *South African M. J.* 10: 599, 1936.
191. Van der Post, C. W. H.: Further Experiences With Pentothal Sodium, *South African M. J.* 12: 421, 1938.
192. Veal, J. R., and Reynolds, Chapman: The Cumulative Effects of Pentothal Sodium, *South. M. J.* 31: 649, 1938.
193. Villar Andrade, Fernando: La anestesia intravenosa por el pentotal sodico, *Rev. mex. de cir., ginec., y cáncer* 6: 47, 1938.
194. Villar Andrade, Fernando: La anestesia en la clinica Mexicana de Cirugia y Radioterapia, *Rev. mex. de cir., ginec., y cáncer* 6: 413, 1938.
195. Villar Andrade, Fernando: La anestesia en la Clinica Mexicana de Cirugia y Radioterapia, *Rev. mex. de cir., ginec., y cáncer* 8: 147, 1940.
196. Villar Andrade, Fernando: La anestesia intravenosa por el pentotal sodico, su aplicación y sus ventajas, *Rev. mex. de cir., ginec., y cáncer* 8: 507, 1940.
197. Volpitto, P. P., and Marangoni, B. A.: Electrocardiographic Studies During Anesthesia With Intravenous Barbiturates, *J. Lab. & Clin. Med.* 23: 575, 1938.
198. Weese, H.: Concerning the Mechanism of Anesthesia Accidents in Sublingual Infections, *Anesth. & Analg.* 18: 15, 1939.
199. Weinstein, M. L.: Rectal Pentothal Sodium: a New Pre- and Basal Anesthetic Drug in the Practice of Surgery, *Anesth. & Analg.* 18: 221, 1939.
200. Werner, H. W.: The Duration of Action of Picrotoxin, Metrazol, and Coramine, *J. Pharmacol. & Exper. Therap.* 63: 39, 1938.
201. Werner, H. W., and Tatum, A. L.: A Comparative Study of the Stimulant Analeptics Picrotoxin, Metrazol, and Coramine, *J. Pharmacol. & Exper. Therap.* 66: 260, 1939.
202. Westell, U. M.: Anesthesia for Chest Injuries, *Lancet* 2: 761, 1940.
203. Wilcox, F. C., and Tovell, R. M.: Anesthesia in Relation to Diabetes, *Anesth. & Analg.* 18: 94, 1939.
204. Williams, A. C.: Ludwig's Angina, *Surg., Gynec. & Obsf.* 70: 140, 1940.
205. Woodbridge, P. D.: Recent Experiences and Present Practice in Anesthesia, *S. Clin. North America* 18: 863, 1938.
206. Wright, A. D.: Technique of Evipan Anesthesia, *Lancet* 1: 1040, 1935.
207. Zierold, A. A.: Gangrene of the Extremity in the Diabetic, *Ann. Surg.* 110: 723, 1939.
208. Zuckermann, C.: Pentothal Sodium Intravenously, *Rev. mex. de cir., ginec., y cáncer* 7: 503, 1939.
209. Zuckermann, C., and Villar Andrade, Fernando: El pentotal sodico en cirugia mayor, *Rev. mex. de cir., ginec., y cáncer* 6: 287, 1938.

152. Report of Council on Pharmacy and Chemistry of A. M. A.: Present Status of Picrotoxin in Poisoning by the Barbiturates, *J. A. M. A.* 112: 431, 1939.
153. Reynolds, Chapman: Dangers of Prolonged Pentothal Sodium Anesthesia From the Pharmacological Standpoint, *Anesth. & Analg.* 18: 270, 1939.
154. Reynolds, Chapman, Schenken, J. R., and Veal, J. R.: Pathological Findings in Mice After Pentothal Narcosis, *Anesth. & Analg.* 17: 357, 1938.
155. Reynolds, Chapman, and Veal, J. R.: Circulatory Effects of Pentothal Sodium, *Proc. Soc. Exper. Biol. & Med.* 37: 627, 1937-1938.
156. Reynolds, Chapman, and Veal, J. R.: Circulatory Versus Respiratory Deaths From Pentothal Sodium, *South. M. J.* 31: 650, 1938.
157. Rivett, L. C., and Quayle, G.: A Method of Administering Continuous Intravenous Anesthesia for Abdominal Surgery, *Proc. Roy. Soc. Med.* 33: 631, 1940.
158. Robbins, B. H.: Preanesthetic Medication, *Arch. Surg.* 40: 1044, 1940.
159. Ruth, H. S., Tovell, R. M., Milligan, A. D., and Charleroy, D. K.: Pentothal Sodium—Is Its Growing Popularity Justified? *J. A. M. A.* 113: 1864, 1939.
160. Sankey, B. R., and Russell, K. S.: Anesthesia for Traumatic and Industrial Surgery, *Anesth. & Analg.* 19: 169, 1940.
161. Scheifley, C. H., and Higgins, G. M.: The Effect of Partial Hepatectomy on the Action of Certain Barbiturates and a Phenylurea Derivative, *Am. J. M. Sc.* 200: 264, 1940.
162. Schindler, R.: Results of a Questionnaire on Fatalities in Gastrosocopy, *Am. J. Digest. Dis.* 7: 293, 1940.
163. Schoenewald, G., and Schweitzer, A., and Steel, G. C.: Action of Veritol in Blood Pressure and Heart Under Various Anesthetics, *Lancet* 1: 544, 1940.
164. Schube, Purcell G.: A Study of the Use of Coramine in Dealing With the Effects of Barbituric Acid Derivatives, *New England J. Med.* 214: 926, 1936.
165. Sellman, P.: Preoperative Medication, *S. Clin. North America* 20: 621, 1940.
166. Selman, W. A.: Discussion of Davison and Rudder.<sup>38</sup>
167. Shackleford, B. L.: Discussion of Davison and Rudder.<sup>38</sup>
168. Sise, L. F.: General Anesthesia, *New England J. Med.* 220: 667, 1939.
169. Sise, L. F.: The Management of the Patient Under Spinal Anesthesia, *Surg. Clin. North America* 20: 631, 1940.
170. Sise, L. F., and Ford, E. J.: Intravenous Anesthesia, *S. Clin. North America* 16: 1713, 1936.
171. Smith, C. H.: Use of Sodium Pentothal Anesthesia for a Patient With a Tendency to Thrombosis and Embolism, *Proc. Staff Meet., Mayo Clin.* 12: 239, 1937.
172. Smith, E. J. R.: Use of Sulfur-Containing Compounds, Particularly Pentothal Sodium in Conjunction With Sulfapyridine, *Brit. M. J.* 2: 488, 1940.
173. Smith, Hugh: Discussion of Porter.<sup>146</sup>
174. Smithwick, Gladys: Pentothal Sodium for Intravenous Anesthesia, *Kentucky M. J.* 36: 427, 1938.
175. Solomons, Edward: Pentothal Sodium in Obstetrics, *Irish J. M. Sc.* 6: 746, 1936.
176. Somersfield, Ralph, and Tovell, R. M.: Case Report: Successful Treatment of Hysterical Paralysis With Pentothal Sodium and Psychotherapy, *Anesthesiology* 2: 59, 1941.
177. Steel, G. C.: The Use of Pentothal Acid in Midwifery, *Lancet* 2: 251, 1939.
178. Special Article: The Pain of Labour, *Lancet* 1: 888, 1939.
179. Tabern, D. L., and Volwiler, E. H.: Sulphur Containing Barbiturate Hypnotics, *J. Am. Chem. Soc.* 57: 1961, 1935.
180. Thomas, G. J.: Clinical and Laboratory Observations on Intravenous Anesthesia, *Anesth. & Analg.* 17: 163, 1938.
181. Thomas, G. J.: Discussion of Ruth et al.<sup>159</sup>
182. Thomas, G. J.: Anesthetist Takes Issue, *Pittsburgh M. Bull.* 29: 434, 1940.
183. Thompson, G. J.: Transurethral Surgery in 1934, *Proc. Staff Meet., Mayo Clin.* 10: 220, 1935.
184. Thompson, G. J.: Transurethral Surgery in 1935, *Proc. Staff Meet., Mayo Clin.* 11: 360, 1936.

on the ureteropelvic junction for stenosis (Y-plasty of Foley and others), 20 cases; (c) resection of renal pelvis and reimplantation of ureter, 10 cases.

McIver stated the purpose of all these operations was to refunnel the pelvic outlet. He demonstrated many valuable technical points, including the use of a "blowout patch" of fat to seal a defect rather than an overabundance of sutures; the use of a nephrostomy tube and ureteral catheter splint for ten days to three weeks after the plastic and the reimplanting operation; the necessity for complete lysis of adhesions, bands, and vessels at the junction, after which, if obstruction still remains due to stricture, a plastic must be done; the combining of a nephropexy to provide suitable postural drainage along with the corrective operation; and finally systematic cystoscopic dilatation and lavage in subsequent treatment.

Next Louis M. Orr, Jr., in association with P. R. Kundert, Orlando, Fla., discussed Renal Counterbalance in Relation to Conservative Renal Surgery. Orr reviewed Hinman's theory of counterbalance, which states that, granted a normal kidney and a hydronephrotic kidney of sufficiently long standing so that its function has been assumed by the normal kidney, anatomic relief of the hydronephrotic kidney will not be followed by its functional recovery. Orr presented a personal case in substantiation of Hinman's theory in which satisfactory anatomic regression of a hydronephrotic kidney following a plastic procedure was not accompanied by recovery of function. A moderate hypertension developed also. Orr concluded that the ability of a hydronephrotic kidney to recover could be tested by retention catheters and functional tests. Perhaps nephrectomy might be preferable in some cases rather than conservative surgery.

Thomas D. Moore, Memphis, Tenn., presented Late Results in Plastic Surgery in Hydronephrosis. Factors involved in the choice of cases for this type of surgery include the age and life expectancy of the patient, the possibility of future childbearing, the economic status, the ability to clear up or control urinary tract infection, and the type of obstruction.

In 18 cases (2 bilateral) of noncalculous hydronephrosis operated upon by Moore and followed for from seven months to ten years, there was no operative mortality; the ages were from 7 to 70 years; there were 2 failures with subsequent nephrectomy and another developed a stag-horn calculus six years after operation. Best results were obtained in 10 cases of high insertion of the ureter, where only 1 failure occurred. In 6 cases of aberrant vessel, section of the vessel alone in 6 instances was disappointing.

Moore said a word in favor of the Rammstedt incision for ureteropelvic junction stricture. He had found reimplantation of the ureter gratifying. Long nephrostomy drainage and splinting (e.g., six weeks) was advocated in some cases.

In general, late results of conservative surgery were 80 per cent good and 20 per cent unsatisfactory.

Discussion of this symposium settled largely around the question of counterbalance. C. E. Burford, St. Louis, and R. E. Van Duzen, Dallas, questioned its clinical application. In regard to the conservative surgery, Van Duzen would prefer to do a plastic procedure, but if it were not feasible, he personally would do a nephrectomy rather than attempt reimplantation.

4. Ureterointestinal Implantation: Experimental and Clinical Results With a New Method, Hugh J. Jewett, Baltimore, Md.—The operation is carried out in two stages. Stage I: Abdomen opened in midline; ureters freed up from pelvic brim downward; each buried in a furrow along the corresponding side of the sigmoid and abdomen closed. The ureters are not severed and the urinary stream is not diverted. Stage II: After two weeks or longer, abdomen reopened; ureters distal to implantation severed and segment attached to bladder tied and allowed to retract; a special insulated electrode devised by Jewett is inserted into open end of implanted ureter, current applied and electrode plunged into bowel; end of ureter now treated as appendix stump by burying in bowel wall.

# Review of Recent Meetings

## MEETING OF THE UROLOGICAL SECTION OF THE SOUTHERN MEDICAL ASSOCIATION, ST. LOUIS, MO., NOVEMBER 12 AND 13, 1941

HARRY M. SPENCE, M.D., DALLAS, TEX.

THE Urological Section of the Thirty-Fifth Annual Meeting of the Southern Medical Association met November 12 and 13, 1941, in St. Louis. The following program was given:

1. **Renal Cortical Necrosis: Case Reports**, Fred K. Garvey, Winston-Salem, N. C.—Forty-two cases of this entity were reported in 1934 and forty-seven additional cases have been recorded in the last seven years, showing it is of clinical importance. While there are exceptions, it occurs typically in pregnant multiparas over 35 years of age and is characterized by renal pain, nausea and vomiting, edema, anuria, and death. The anuria, which is the most striking symptom, comes on suddenly after delivery in a patient with no previous urinary abnormalities. Cystoscopic examination, including retrograde pyelography, is negative. The etiology is unknown, but the pathology consists in a thrombosis restricted to the terminal lobular arteries of the kidney with coagulation necrosis of the renal cortex. Garvey has seen three cases, all following delivery. The first patient was anuric for seventeen days before death. In the second, the N.P.N. reached 200 mg. per 100 c.c. of blood before death on the tenth day. The patient in his final case passed no urine for five days before dying. These cases showed normal pyelograms; autopsy revealed the cortical necrosis.

In the discussion, J. C. Pennington, Nashville, Tenn., reported a case in a newborn simulating this malady. Another discussant felt that probably some cases diagnosed as eclampsia are actually cases of renal cortical necrosis.

2. **The Technique of Pyelography**, H. McClure Young, Columbia, Mo.—Young presented his method in detail, the essentials of which are the use of a 10 c.c. piston syringe and slow injection of the pyelographic medium with cessation of injection at any facial expression of discomfort by the patient. He does one side at a time. He emphasized the necessity for cooperation by patient, x-ray technician, and doctor.

J. U. Reaves, Mobile, Ala., and H. K. Wade, Hot Springs, Ark., reiterated that gentleness is the watchword in pyelography. They felt there was no valid objection to making a bilateral pyelogram on the same plate. H. M. Spence, Dallas, stated that air pyelograms were not used as generally as their value would warrant. In a fairly extensive experience with the method, he has been convinced of its safety and value, particularly in stone cases. Also in the dispensary patients, it had an economic advantage because the flat plate and pyelogram could be combined on one film.

3. In a **Symposium on Conservative Renal Surgery**, R. B. McIver, Jacksonville, Fla., spoke first on **Plastic Procedures for the Correction of Defective Renal Drainage**. He confined his remarks to the surgical correction of significant ureteropelvic obstruction and presented clear-cut motion pictures of his technique. In a series of 100 such cases, he carried out conservative operations as follows: (a) disposal of fibrous bands, adhesions, and aberrant vessels, 70 cases; (b) plastic operation

a traction suture of catgut passing through the gubernaculum or lower pole of the testicle out through the scrotal sac and being tied to the skin of the thigh. This suture absorbs in a week or so after all danger of retraction of the testicle has passed. He described a case of cryptorchidism in which he found the testicle in the neighborhood of the kidney and was able to bring it down to its normal position after severing all blood supply except the artery of the vas and the vas itself, and have the testicle remain viable. This fortunate result is a marked exception to the general rule.

Lowsley reported 15 per cent success in his hands of Hagner's operation of anastomosing the vas to the upper pole of the epididymis in cases of sterility due to occlusion of the genital passageways following epididymitis.

Lowsley gave follow-up results of the operation he has devised for impotence, which consists of plicating the ischiocavernosus and bulbocavernosus muscles with his ribbon catgut through a perineal incision. Of 143 cases, he was able to follow personally, 67 per cent were considered successful, 22 per cent improved, and 11 per cent unchanged. The most suitable cases for operation are the ones following some traumatism to the perineum. In the individual with atrophied perineal musculature, subsequent to early hypersexual activity, it is also indicated. He was emphatic in his insistence that this is not an operation for old men or psycho-neurotics and should be done only after exhaustive preoperative study and observation.

A motion picture showing Lowsley's operation for hypospadias was presented. This is well illustrated in his recent textbook. He has treated approximately fifty cases by this method with good results. He prefers to do the procedure shortly before puberty. Some idea of the patience required in this type of case is shown by a patient on whom seventeen separate operations were necessary before an ultimate excellent result was achieved.

9. Grayson Carroll, St. Louis, delivered the Chairman's Address entitled *Urological Investigational Work in the South*, in which he summarized the original investigations in all fields of urology by the membership. In answer to questionnaires sent out to twenty-five representative members, he found that adequate facilities exist for investigational work, but most men met the expenses of their investigations wholly or in part out of their own pockets. Carroll pointed out the advantages of having endowed research institutes, including funds from commercial firms and foundations supported by royalties from medical patients, to make further investigations. He urged urologists to use their influence in appropriate ways to found institutes for research.

10. Jarratt P. Robertson, Birmingham, Ala., spoke on *Renal Injury*, presenting his observations on 26 cases. The series included 25 males and 1 female. Causative factors included: automobile accidents, 12; penetrating wounds (knives, gunshot, ice pick), 6; falls, 3; football injuries, 2. The pathology varied from contusions to lacerations and frank rupture. The predominant symptom was hematuria, which was present in over 90 per cent of the cases, while shock, renal pain and tenderness, and injuries to other viscera were noted frequently.

In regard to diagnostic measures, Robertson favors cystoscopy and retrograde pyelography as most valuable in showing early the extent of the damage and laying the basis for proper treatment. He feels that the excretory urogram is not of much value in these cases due to suppression of urine from the attendant shock and impaired renal secretion and that the dangers of sepsis following cystoscopy and retrograde examination have been exaggerated.

Robertson emphasized that the treatment depends on the general condition of the patient as regards shock, associated injuries, and the extent of the renal damage shown on retrograde pyelography. He recommends trying conservative treatment first, including bed rest for two weeks after cessation of the hematuria. Frequent checkups are necessary in cases treated conservatively. His rule in the

Jewett has done the operation in numerous dogs and several human beings. Excretory urograms and autopsy specimens attest to the value of the method in avoiding sepsis and constriction of ureteral opening.

H. A. O'Brien, Dallas, evaluated the method favorably as combining the best features of several preceding methods. His only theoretical objection was that the final opening in the ureter was in its lateral wall rather than its open end.

5. **Sulfathiazole Therapy in Venerology**, A. A. Creecy and H. L. Switkes, Newport News, Va.—Creecy reviewed an extensive experience with hospitalized young males in which various dosage schedules were used. The diagnoses included gonorrhea, nonspecific urethritis, and chancroid. He concluded that the drug was very effective in all these conditions. Large initial and total doses in the hospitalized group were somewhat more effective than moderate doses. Sulfathiazole blood level determinations were not particularly helpful. Creecy has had opportunity to study sulfadiazine also, and he feels that sulfathiazole is somewhat more toxic than sulfadiazine but no less efficacious.

7. **Preoperative Use of Sulfathiazole for the Prevention of Postoperative Complications: A Clinical Study**, J. A. C. Colston, with R. W. Satterthwaite, Baltimore, Md.—In spite of all the usual precautions, infection still remains a hazard in operations on the genitourinary tract. It has occurred to many that having a sulfonamide concentration present in the body at the time of operation might prevent the growth of bacteria already present and the ingress of others following the operation. Thus Hugh Young and his co-workers have reported on the preoperative use of sulfathiazole in fourteen plastic operations on the genitals in which it was evident that healing occurred more quickly and with less danger of sepsis.

In order to determine the value of sulfathiazole administered preoperatively as a prophylactic against postoperative complications, Colston, over the past eighteen months, used the drug routinely in a series of 112 urological cases where infection was already present or where the urinary tract was to be opened and compared the results with a corresponding control series in which the drug was not used. A dose of 2 to 4 Gm., averaging 3 Gm. a day, was administered for a preoperative interval of forty-eight hours, including a dose on the morning of operation. Colston felt this dosage and interval gave a maximum protective effect with a minimum of toxicity. The postoperative temperature chart was used as the index of morbidity.

In the group which had received sulfathiazole preoperatively, the temperature reactions were consistently lower in the first four postoperative days than in the control series. This was particularly noteworthy on the third and fourth days, when elevated temperature means serious sepsis. Furthermore, no pneumonia or blood stream infection occurred in the sulfathiazole-treated series in distinct contrast to the control group.

8. **Oswald S. Lowsley**, New York City, was the guest speaker, selecting as his subject **Plastic Operations in Urology**. He presented many illustrated cases. For exertional incontinence in women, he has modified the classic Kelly operation of plicating the base of the urethra and bladder neck by making an incision superior to the external meatus and plicating the roof of the urethra with ribbon catgut. He has similarly plicated the perineal musculature and rectal wall through a perineal exposure in a few cases of incontinence of urine and feces due to spinal bifida with good results. He stated that ribbon catgut contains only  $\frac{1}{4}$  as much catgut as the ordinary twisted variety and possesses the additional advantage of not cutting out of delicate musculatures; it is ultimately replaced by fibroblasts.

For undescended testicle, Lowsley uses a modified **Torch procedure** in which, after lengthening the cord as much as possible by meticulously dissecting away all fibrous bands, adhesions, etc., he replaces the testicle in the scrotum and uses

## Book Reviews

---

**The Treatment of Burns (Oxford War Manuals).** By A. B. Wallace. Pp. 113, with 16 illustrations. London, Humphrey Milford, 1941. Oxford University Press. \$1.25.

This book is the product of the traditional home of advanced thought concerning burns in Scotland—the Royal Hospital for Sick Children and the University of Edinburgh. The important work on burns carried out by Mr. W. C. Wilson during the decade 1928 to 1938 has been continued by the author of the present volume since Mr. Wilson's appointment as Professor of Surgery at the University of Aberdeen. An adequate discussion of the early care of burns followed by insufficient data regarding subsequent plastic management is a weakness inherent in many works on burns. Such is not the case with Wallace's book as he shows evidence of his intensive training in plastic surgery received under Sir Harold Gillies as a part of the British war effort. The book adequately considers all chronologic aspects of the care of a burn case.

Inclusion of diagrams of emergency instrument tables and of practical lists of materials needed for treatment is of value from the standpoint of war use. The nursing care of burns is adequately considered. This is an important item in cases of emergency when large numbers of burns may overwhelm the capacities of the medical staff.

The book begins with chapters on the classification, clinical course, and complications of burns, after which the remaining four-fifths of the material is devoted to treatment itself. The use of tannic acid is not abandoned while indications for more recent treatments such as the Bunyan envelope and the triple dye are listed. The local use of sulfonamide drugs, first described in Great Britain by Wallace himself in an article (Brit. M. J. 1: 469-472, 1941) appearing just as this book went to press, is described in the present text.

One objection to the book might be the space given to special consideration of burns in children. This would seem to be out of place in a war manual, but when it is remembered that in total warfare civilian burns are not infrequent, this objection is not so valid. The book seems to be a succinct review of the present status of burn treatment, and should be of interest to civilian, industrial, and military surgeons.

---

**Anus, Rectum, Sigmoid Colon: Diagnosis and Treatment.** By Harry Ellicott Bacon, B.S., M.D., F.A.C.S., F.A.P.S. Ed. 2. Pp. 857, with 487 illustrations. Philadelphia, 1941, J. B. Lippincott Co. \$8.50.

The second edition of this well-known book gives the medical profession a detailed and comprehensive treatise of all those structures and lesions coming within the preview of the proctologist. In some instances, the strict confines of proctology have been overstepped. Excellent discussions of malignant tumors of the sigmoid colon are included. For this reason, the book is enhanced in value and will be appreciated the more by the general surgeon. No fewer than sixteen different operative procedures for dealing with malignancy of the rectum and sigmoid colon are described. The more common lesions of the anus and rectum are considered in detail in all their phases.



kidneys necessitating operation is to save the patient first and if possible the kidney. Twenty of Robertson's cases were treated conservatively and 7 by operation, including 2 late nephrectomies. He had 4 deaths, 2 being operative cases and 2 nonoperative cases where severe shock contraindicated surgery.

11. **Diagnosis and Treatment of Traumatic Rupture of the Posterior Urethra, C. J. Reynolds, Bluefield, W. Va.**—Reynolds emphasized the value of using the Foley catheter as a splint for the damaged urethra and to pull the severed bladder neck downward. The bladder is opened through a suprapubic incision to facilitate the manipulation and placement of the catheter but is then closed.

12. **Torsion of the Testicle and Its Appendages, Hubert K. Turley, Memphis, Tenn.**—Turley presented 4 cases illustrating this condition. In 1 case of recurrent torsion, he was able to save the testicle and perform an orchiopexy. In 2 other cases, orchidectomy was necessary. In 1 case of torsion of the hydatid of Morgagni, excision of this appendage with preservation of the testicle was done.

Turley emphasized the fact that torsion of the testicle is a surgical emergency if the testicle is to be saved and he urged calling this to the attention of pediatricians. He mentioned the differential diagnosis between torsion and epididymitis (sudden onset of torsion, absence of urinary infection in torsion, pain exaggerated on elevating testicle in torsion; i.e., Prehn's test). It is probable that torsion is not recognized as often as it should be.

The treatment is immediate surgical exploration and detorsion; if the blood supply is not impaired, the testicle is saved and fixed to the scrotum to prevent a recurrence. If blood supply is compromised, orchidectomy is done. Papers 10, 11, and 12 were discussed by **Edgar Burns, New Orleans, La.**, who reported a series of 16 cases of torsion from Charity Hospital, in which 9 orchidectomies were necessary. He felt the clinical picture was the important factor in kidney injuries and determined the course of procedure. **Rubin Flocks, Iowa City, Ia.**, emphasized the importance of late observation and urography in cases of renal injury.

13. **Wm. C. D. McCuskey, Wheeling, W. Va.**, presented **A Résumé of the End Results of 1,000 Consecutive Cases Following Surgery for the Relief of Bladder Neck Obstruction**, extending over the years 1930 to 1941 for his own practice. This series included 958 adult males, 17 children, and 15 women. The indications for surgery included 772 cases of benign hypertrophy, 185 carcinomas, and 27 "cord" bladders. Seventy-five "prophylactic" resections were done. A total of 900 transurethral resections were performed, 60 patients requiring two or more sessions. Originally the Caulk punch was used in a series of 243 cases with 4 deaths, but now the McCarthy resectoscope with the Boye electrosurgical unit is employed for the transurethral work. Radical total perineal prostatectomy was done in several cases after tissue removed by resection showed carcinoma.

From the follow-up of this wealth of material, McCuskey concluded that the operation should be selected for the patient and not vice versa. His results in transurethral resection in Grade IV hypertrophies left something to be desired and he felt that the suprapubic operation entailed no greater risk than two or more resections in this type of case. He was not favorably impressed with the "prophylactic resections." He felt that the use of the resectoscope detected more early carcinomas and broadened the opportunities for total perineal extirpation.

In the discussion, **J. F. Patton, St. Louis**, stated that the aims of bladder neck surgery were (1) to restore function with (2) a low mortality and it was often necessary to strike a balance between the two. It was his belief that 20 per cent of these cases were since best handled by open operation.

**H. L. Tolson, Cumberland, Md.**, stated that a minimum of coagulation led to better results.

# SURGERY

VOL. 11

APRIL, 1942

No. 4

## Original Communications

### MALIGNANT ADENOMA OF THE LUNG

#### CARCINOMA-LIKE TUMORS WITH LONG CLINICAL COURSE

W. E. ADAMS, M.D., PAUL E. STEINER, M.D., AND  
ROBERT G. BLOCH, M.D., CHICAGO, ILL.

*(From the Departments of Surgery, Pathology and Medicine of the  
University of Chicago)*

DURING the past decade the role of carcinoma of the lung has changed from a subject of interest chiefly to pathologists, to a problem of major importance for clinicians. Since 1933 an ever-increasing number of patients have been treated successfully by surgical extirpation of the lung and tumor-bearing tissue. Prior to this period the mortality of the tumor was 100 per cent<sup>1, 2, 3</sup> and a correct diagnosis was frequently lacking until post-mortem examination.

With the development of successful surgical measures for this tumor clinical interest became widespread. Thus it was not appreciated until recent years that the incidence of carcinoma of the lung is about 10 per cent of all malignant tumors or second only to carcinoma of the stomach.<sup>4</sup> It has been estimated that approximately 15,000 deaths occur annually in the United States due to this tumor. Successful surgical therapy has been employed for an insufficient time to allow for future predictions. However, it is probably safe to say that at the present time the outlook for carcinoma of the lung is better than that for carcinoma of the stomach.

This report deals with a particular type of tumor of the lung over which much controversy has continued. Two widely divergent opinions as to their proper management are prevalent at the present time. By one group these tumors are considered benign and are treated as such by bronchoscopic removal.<sup>5, 6</sup> A second group classifies them as malignant and advises treatment by total pneumonectomy.<sup>7</sup>

The marked variability in the clinical course of malignant tumors of the lung in general has helped to confuse an attempt at proper classification and correct management.

The format of the book makes for easy reading and ready reference. The 487 illustrations, which include diagrams, drawings, and photographs, are excellent. Lengthy bibliographies are included at the end of each chapter and cover the world literature up to 1939. A detailed index, both of the authors quoted and subjects covered, is appended.

Without doubt, this book will become a standard and authoritative source in its field.

**Hemorrhagic Diseases: Photo-Electric Study of Blood Coagulability** By Kaare K. Nygaard. Pp 320, with 59 illustrations. St. Louis, 1941, The C. V. Mosby Co. \$5.50

In spite of recent intensive investigations there still exists a lack of trenchant knowledge on the subject of hemorrhagic diseases. This is clearly indicated by the varied and, in many instances, confusing classifications of the multitudinous hemorrhagic manifestations. Obviously investigations which may aid in clarifying some of these problems must be considered desirable. Accordingly this monograph is a distinct contribution.

Realizing that not the least important factor contributing to the confusing character of hemorrhagic diseases has been the lack of reliable procedures of investigation, Nygaard has approached the problem by concentrating on the measurement of the velocity of blood coagulation. This has been accomplished with the application of the photo electric principle which permits a more dependable method of study. The author has applied this investigative procedure to various hemorrhagic diseases and has compiled in this book his results and interpretations.

The book is divided into three parts, the first of which is devoted to a brief review of the various approaches to the measurement of blood coagulation and a description of the photo electric principle and particularly its applicability to the problem of blood coagulation. The second part is divided into three chapters. In the first of these there is presented the results of certain experimental investigations on factors which may influence the coagulability of blood plasma. In the second chapter the author gives a brief review of the prevalent opinions concerning the nature of the thrombin-fibrinogen reaction and an interpretation of his observations with the photo electric principle. A brief review of the character and mechanism of the coagulant effect of thromboplastin and the author's investigations of this subject with the photo electric principle are presented in the third chapter. The third part of the monograph includes six chapters, the first of which is devoted to another classification of hemorrhagic diseases. The results of the author's studies and his interpretations as well as brief reviews of hemophilia, thrombocytopenic purpura, vitamin K deficiency, the hemorrhagic tendency in diseases of the kidney, tract, liver, and pinealis, and hemorrhagic disease of the newborn comprise the other five chapters. Since these are not the only conditions which may be considered in the group of hemorrhagic diseases the criticism that the title is misleading may be applied. Apparently, however, the author's purpose was not a complete review of the subject of hemorrhagic diseases but rather an exposition of this new approach of investigation and an interpretation of the results of his observations in the more common forms of these diseases. In this respect the book is a distinct and commendable contribution to the subject and deserves careful consideration particularly by investigators interested in the varied and bewildering disturbances of blood coagulation.

pyema or bronchial fistula complicating the operation. The patient gained quite rapidly in weight and strength and her symptoms were entirely alleviated. She has remained well up to the present time.

*The Tumor and the Right Lower Lobe.*—The surgically excised right lower lobe contained a tumor mass which was about 2 cm. in diameter (Fig. 1*A*). It was located at the junction of a branch with the main bronchus, into which it also projected. It filled and dilated the bronchus in which it arose and to whose wall it was attached by a broad base. On section the tumor was firm and white. The remainder of this lobe showed bronchiectasis, total atelectasis, and fibrous pleural adhesions. It was markedly shrunken, solid and contained little air. Purulent material filled the markedly dilated bronchi.

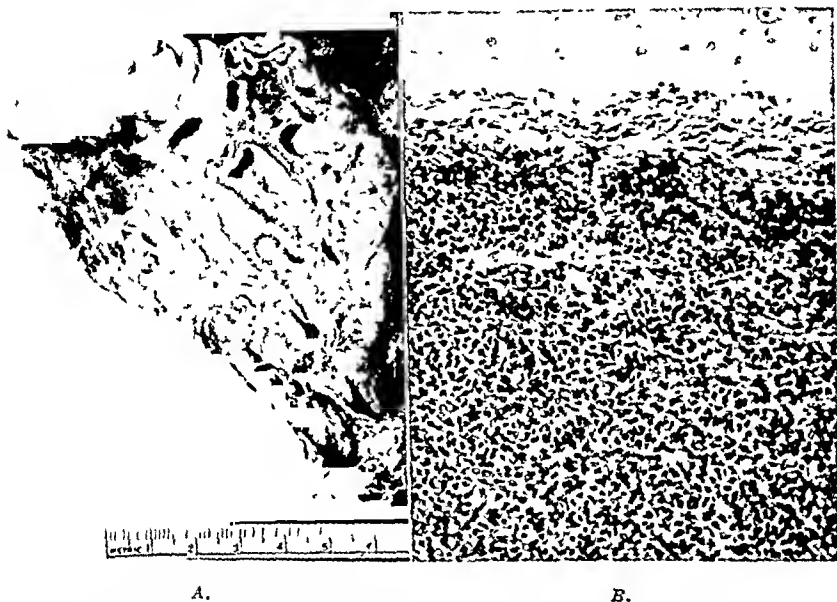


Fig 1—Case 1 W. W. A. Photograph of the excised lung showing the intra-bronchial tumor, with bronchiectasis and atelectasis distal to this point of obstruction. B Photomicrograph ( $\times 165$ ) showing the histology of the tumor and its infiltration into bronchial cartilage. Many areas, unlike this, were distinctly papillary or alveolar. Connective tissue stains reveal more stroma in this region than would be suspected from this illustration.

Microscopically the tumor was composed of uniform small polyhedral cells with hyperchromatic, round nuclei and a scanty amount of acidophilic cytoplasm. Mitotic figures were not seen. The cells were arranged on a fine fibrous stroma which had a reticulated pattern, thus producing an alveolar appearance of the epithelial cells. This tumor infiltrated its bronchus at the point of attachment, penetrating into the bronchial cartilage. (Fig. 1*B*.) The free surface of the tumor was capped by a layer of fibrous connective tissue, and this was covered, where not ulcerated, by stratified squamous epithelium. The deep portion of the tumor was separated from lung parenchyma by a less perfect layer of connective tissue.

CASE 2.—L. M. (No 175341), a white male, 37 years of age, was admitted the hospital on July 9, 1937, complaining of a chronic cough for three years, voice for three weeks and a continuous "run down" feeling for the months. The patient enjoyed perfect health until four years before and he began to have upper respiratory infections. Following this he had a productive cough which came on in attacks four

This is especially true with the group of cases under discussion. Clinically they behave like benign tumors for months or years, giving rise to symptoms only by obstruction of the air passages. Ultimately they show definite evidence of malignancy by involvement of adjacent structures by direct extension and by distal metastases although few or no mitotic figures are demonstrable.

#### REPORT OF CASES

CASE 1.—W. W. (No. 226258), a white female, 33 years of age, entered the hospital on Aug. 18, 1939, complaining of a persistent cough with repeated "colds" for five years, and repeated severe attacks of hemoptysis for four months. The cough had been somewhat more pronounced during the winter months and often her sputum had a brownish tinge. On April 29, 1939, the patient had a severe hemoptysis. She was in a hospital for one month with a diagnosis of pneumonia of the right lower lobe. Five days after discharge, she felt ill and her temperature was 101°. X-rays of the chest were made and her condition diagnosed as "bronchiectasis." After three weeks in a sanatorium she was "much improved." The next severe hemorrhage was on July 31 when she "coughed up a teacup full of blood." A bronchoscopic examination with biopsy of a tumor mass in the right lower lobe bronchus was made but a definite diagnosis was impossible. Her hemoptysis gradually subsided until one week before admission when it recurred in severe form and continued until admission to the hospital. The bloody sputum had recently become foul. The patient had lost fifteen pounds in the past two years and had become weaker and developed some dyspnea with the repeated hemoptyses and attacks of fever. She stated that she had had an attack of pneumonia two years before admission.

Physical examination revealed an anemic, chronically ill appearing white female who raised sputum tinged with old blood on frequent coughing. Her temperature and pulse were normal. The abnormal physical findings were limited to the chest. Expansion of the right side was somewhat diminished. There was an area of dullness over the region of the right lower lobe. The breath sounds over this area were decreased. Tactile fremitus was unchanged. There were no rales. The blood pressure was 105/70.

*Laboratory Examination.*—The blood revealed a hemoglobin of 47 per cent; R.B.C., 3,30; and W.B.C., 7,550. The sputum was grossly bloody. On staining it presented no evidence of tubercle bacilli and on culture revealed *Streptococcus haemolyticus*, *Str. viridans*, *Staphylococcus aureus* and pneumococci. The Wassermann and Kahn tests were normal. An x-ray of the chest revealed an ill-defined opacity in the right lower lung field. When this was repeated following the introduction of iodized oil, an obstruction of the right lower lobe bronchus was demonstrated. Bronchoscopy revealed a tumor in the right lower lobe bronchus which bled freely when a piece was removed for microscopic examination. Clinical diagnosis: bronchogenic tumor of right lower lobe.

The patient was given a blood transfusion in preparation for operation. Because of the positive throat culture of hemolytic streptococcus, she was given a course of sulfanilamide, however, without altering the culture. Because her condition was not emergent, she was allowed to return home, hoping that the streptococcal infection would subside. She was readmitted two months later in approximately the same condition and was found to have a persistent *Str. haemolyticus* infection of the respiratory tract. After hospitalization for ten days a right lower lobectomy was performed. Her convalescence was entirely uneventful, no em-

pyema or bronchial fistula complicating the operation. The patient gained quite rapidly in weight and strength and her symptoms were entirely alleviated. She has remained well up to the present time.

*The Tumor and the Right Lower Lobe.*—The surgically excised right lower lobe contained a tumor mass which was about 2 cm. in diameter (Fig. 1*A*). It was located at the junction of a branch with the main bronchus, into which it also projected. It filled and dilated the bronchus in which it arose and to whose wall it was attached by a broad base. On section the tumor was firm and white. The remainder of this lobe showed bronchiectasis, total atelectasis, and fibrous pleural adhesions. It was markedly shrunken, solid and contained little air. Purulent material filled the markedly dilated bronchi.

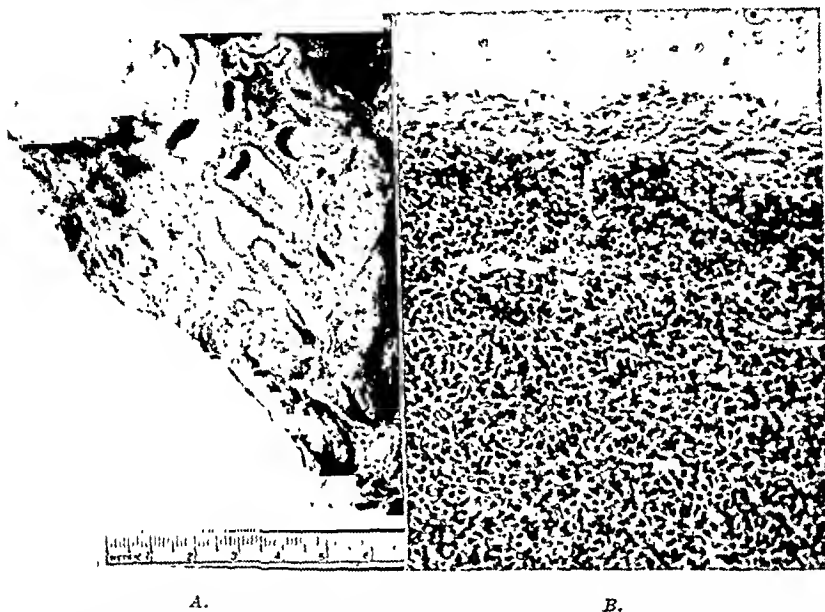


Fig. 1.—Case 1. W. W. A. Photograph of the excised lung showing the intra-bronchial tumor, with bronchiectasis and atelectasis distal to this point of obstruction. B. Photomicrograph ( $\times 165$ ) showing the histology of the tumor and its infiltration into bronchial cartilage. Many areas, unlike this, were distinctly papillary or alveolar. Connective tissue stains reveal more stroma in this region than would be suspected from this illustration.

Microscopically the tumor was composed of uniform small polyhedral cells with hyperchromatic, round nuclei and a scanty amount of acidophilic cytoplasm. Mitotic figures were not seen. The cells were arranged on a fine fibrous stroma which had a reticulated pattern, thus producing an alveolar appearance of the epithelial cells. This tumor infiltrated its bronchus at the point of attachment, penetrating into the bronchial cartilage. (Fig. 1*B*.) The free surface of the tumor was capped by a layer of fibrous connective tissue, and this was covered, where not ulcerated, by stratified squamous epithelium. The deep portion of the tumor was separated from lung parenchyma by a less perfect layer of connective tissue.

CASE 2. —L. M. (No. 178341), a white male, 37 years of age, was admitted the hospital on July 9, 1937, complaining of a chronic cough for three years, voice for three weeks and a continuous "run-down" feeling for the months. The patient enjoyed perfect health until four years before when he began to have upper respiratory infections. Following this he had a productive cough which came on in attacks four to six times

This is especially true with the group of cases under discussion. Clinically they behave like benign tumors for months or years, giving rise to symptoms only by obstruction of the air passages. Ultimately they show definite evidence of malignancy by involvement of adjacent structures by direct extension and by distal metastases although few or no mitotic figures are demonstrable.

#### REPORT OF CASES

CASE 1.—W. W. (No. 226258), a white female, 33 years of age, entered the hospital on Aug. 18, 1939, complaining of a persistent cough with repeated "colds" for five years, and repeated severe attacks of hemoptysis for four months. The cough had been somewhat more pronounced during the winter months and often her sputum had a brownish tinge. On April 29, 1939, the patient had a severe hemoptysis. She was in a hospital for one month with a diagnosis of pneumonia of the right lower lobe. Five days after discharge, she felt ill and her temperature was 101°. X-rays of the chest were made and her condition diagnosed as "bronchiectasis." After three weeks in a sanatorium she was "much improved." The next severe hemorrhage was on July 31 when she "coughed up a teacup full of blood." A bronchoscopic examination with biopsy of a tumor mass in the right lower lobe bronchus was made but a definite diagnosis was impossible. Her hemoptysis gradually subsided until one week before admission when it recurred in severe form and continued until admission to the hospital. The bloody sputum had recently become foul. The patient had lost fifteen pounds in the past two years and had become weaker and developed some dyspnea with the repeated hemoptyses and attacks of fever. She stated that she had had an attack of pneumonia two years before admission.

Physical examination revealed an anemic, chronically ill appearing white female who raised sputum tinged with old blood on frequent coughing. Her temperature and pulse were normal. The abnormal physical findings were limited to the chest. Expansion of the right side was somewhat diminished. There was an area of dullness over the region of the right lower lobe. The breath sounds over this area were decreased. Tactile fremitus was unchanged. There were no rales. The blood pressure was 105/70.

*Laboratory Examination.*—The blood revealed a hemoglobin of 47 per cent; R.B.C., 3,30; and W.B.C., 7,550. The sputum was grossly bloody. On staining it presented no evidence of tubercle bacilli and on culture revealed *Streptococcus haemolyticus*, *Str. viridans*, *Staphylococcus aureus* and pneumococci. The Wassermann and Kahn tests were normal. An x-ray of the chest revealed an ill-defined opacity in the right lower lung field. When this was repeated following the introduction of iodized oil, an obstruction of the right lower lobe bronchus was demonstrated. Bronchoscopy revealed a tumor in the right lower lobe bronchus which bled freely when a piece was removed for microscopic examination. Clinical diagnosis: bronchogenic tumor of right lower lobe.

The patient was given a blood transfusion in preparation for operation. Because of the positive throat culture of hemolytic streptococcus, she was given a course of sulfanilamide, however, without altering the culture. Because her condition was not emergent, she was allowed to return home, hoping that the streptococcal infection would subside. She was readmitted two months later in approximately the same condition and was found to have a persistent *Str. haemolyticus* infection of the respiratory tract. After hospitalization for ten days a right lower lobectomy was performed. Her convalescence was entirely uneventful, no em-

Microscopic examination disclosed that the tumor was composed of fairly uniform small cuboidal to low columnar epithelial cells arranged diffusely or abutting on small cores of connective tissue stroma bearing small blood vessels. The cells were fairly uniform, appearing round to oval, and had hyperchromatic nuclei in which the chromatin pattern was diffuse except for a little clumping. Mitotic figures were not seen. The cytoplasm was scanty, clear, and slightly eosinophilic. The arrangement of the cells about numerous small connective tissue strands, from which the cells tended to shrink, gave the tumor, when first seen superficially, a pseudoadenomatous appearance, whereas it was truly an infinitely complex, solid, papillary structure. There was no evidence of secretion by the cells and there were no true gland lumina. Degenerative changes were absent. (Figs. 2B and 2C.)



Fig. 2A—Case 2. L. M. Photograph showing the polypoid intrabronchial tumor in the lower lobe with bronchiectasis and atelectasis distal to the tumor.

This solid tumor, then, filled the bronchus, which it dilated. The bronchial wall was fairly normal. The free surface of the tumor was composed, in most places, of a dense fibrous connective tissue. At its base the tumor infiltrated the bronchial wall. It denuded and destroyed superficial areas in the cartilage plates, and it bulged outward between cartilage plates into the peribronchial connective tissue. Bronchial lymph nodes and large blood vessels in proximity to this tumor extension were not involved.

The lung distal to the tumor showed a remarkable bronchiectasis. The walls of the bronchi were increased in size and their mucous membrane having been replaced by a granulation tissue. The lung parenchyma in this region showed complete atelectasis. Many alveoli had collapsed.



from two to three weeks. During these attacks he would lose weight and develop a fever, regaining the weight between the attacks. On one occasion the temperature was taken and found to be 104°. During the last year, he gradually began raising sputum, somewhat thick and yellow in character. To his knowledge this had never been foul. His last attack began three weeks before admission and sputum raised was found to be somewhat blood stained. Also, with this last attack, his voice became hoarse. Due to the intensity of his cough, vomiting was present during the last attack. There had been no dyspnea nor chest pain, except on one occasion two years ago and this was only temporary.

Physical examination revealed a well-developed and well-nourished white male who exhibited a frequent nonproductive cough but who did not appear acutely ill. The abnormal findings were limited to the chest and these were not remarkable. Tactile fremitus was increased over the right apical region and was decreased over the left base. The percussion note was somewhat dull at the right apex and markedly dull over the entire left base. The breath sounds here were very much diminished or completely absent. A few, scattered crepitant râles were heard over the lower portion of the left base. The cardiac borders were within normal limits. The blood pressure measured 110/70. There was no clubbing of the finger tips.

*Laboratory Examination.*—The blood revealed hemoglobin of 90 per cent; R.B.C., 5,18; and W.B.C., 9,500. The urine was normal as were the Wassermann and Kahn tests. The sputum showed no evidence of tubercle bacilli. X-rays of the chest revealed an ill-defined opacity involving the lower one-half or two-thirds of the left lung field. It appeared to involve the left lower lobe but did not obliterate the costophrenic angle. The x-ray diagnosis was pneumonia or pulmonary abscesses in the left lower lobe, but it was impossible to rule out atelectasis due to tumor of the left lower lobe bronchus. Bronchoscopic examination revealed a tumor located in the left lower lobe bronchus. This was quite friable and bled freely when biopsied for microscopic examination. It was diagnosed as a basal-cell carcinoma.

Since there was no evidence of metastases or marked local extension a pneumonectomy was advised. On Sept. 8, 1937, the left pleural space was explored and the entire left lower lobe found to be extremely adherent to the chest wall. On mobilizing the left lower lobe, a considerable degree of shock was produced and it was deemed advisable to divide the operation into two stages, according to the Rienhoff<sup>20</sup> technique. The left pulmonary artery was isolated and divided between ligatures and the wound was closed with closed drainage of the pleural space. The patient had a stormy postoperative course and developed a *St. haemolyticus* empyema and a fulminating infection of the chest wall. Supportive measures, such as blood transfusion, intravenous fluids, and multiple thoracotomies maintained the patient in a fairly good condition for the following ten days, after which he became worse and died fourteen days following the operation of generalized sepsis and a fulminating infection of the chest wall.

*The Tumor and Lung.*—(Autopsy No. 4215; Prosecutor, Dr. Walter A. Stryker.) An egg-shaped tumor, 22 by 14 by 10 mm., occluded one of the secondary bronchi near its origin, in the left lower lobe. This tumor was attached at one point by a broad base to the bronchial wall; at other points it was free. It enlarged its own bronchus and by pressure it seemed to have occluded neighboring bronchi. On section the tumor was solid white, and it appeared to have infiltrated the bronchial wall at its base.

The lung lobe containing the tumor was reduced in size. The lung distal to the tumor was flabby and atelectatic, and the bronchi distal to the tumor showed a remarkable dilatation, being up to 1 cm. in diameter. They contained yellowous. (Fig. 2d).

Microscopic examination disclosed that the tumor was composed of fairly uniform small cuboidal to low columnar epithelial cells arranged diffusely or abutting on small cores of connective tissue stroma bearing small blood vessels. The cells were fairly uniform, appearing round to oval, and had hyperchromatic nuclei in which the chromatin pattern was diffuse except for a little clumping. Mitotic figures were not seen. The cytoplasm was scanty, clear, and slightly eosinophilic. The arrangement of the cells about numerous small connective tissue strands, from which the cells tended to shrink, gave the tumor, when first seen superficially, a pseudoadenomatous appearance, whereas it was truly an infinitely complex, solid, papillary structure. There was no evidence of secretion by the cells and there were no true gland lumina. Degenerative changes were absent. (Figs. 2B and 2C.)



Fig. 2A.—Case 2. L. M. Photograph showing the polypoid intrabronchial tumor in the lower lobe with bronchiectasis and atelectasis distal to the tumor.

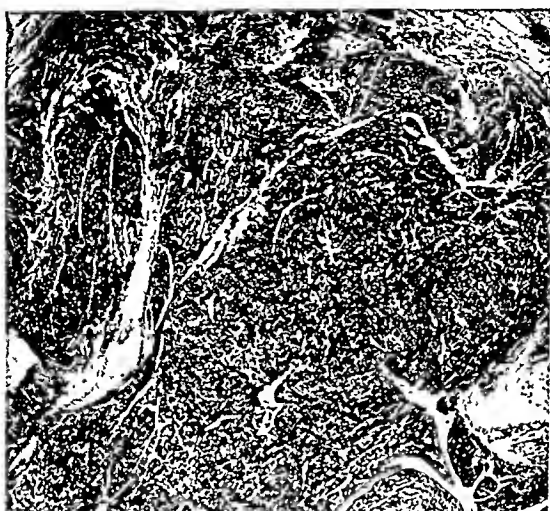
This solid tumor, then, filled the bronchus, which it dilated. The bronchial wall was fairly normal. The free surface of the tumor was composed, in most places, of a dense fibrous connective tissue. At its base the tumor infiltrated the bronchial wall. It denuded and destroyed superficial areas in the cartilage plates, and it bulged outward between cartilage plates into the peribronchial connective tissue. Bronchial lymph nodes and large blood vessels in proximity to this tumor extension were not involved.

The lung distal to the tumor showed a remarkable bronchiectasis. The lumens of the bronchi were increased in size and their mucous membrane was missing, having been replaced by a granulation tissue. The lung parenchyma in this region showed complete atelectasis. Many alveoli had a cuboidal epithelial

lining and there were areas of fibrosis, nodular aggregates of lymphocytes, and occasional giant cells, all associated with the chronic pneumonitis.

There were no gross or microscopic tumor metastases.

B.



C.

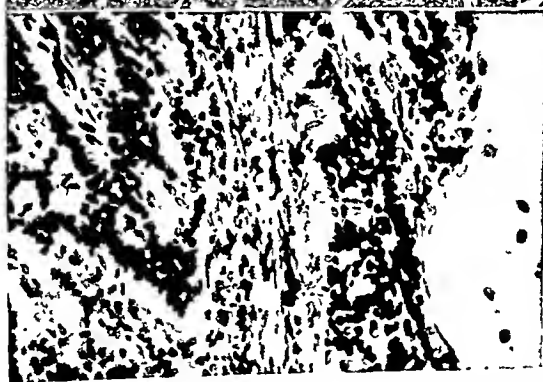


Fig. 2 B and C.—Case 2. B Photomicrograph ( $\times 20$ ) showing the intrabronchial tumor growing outward between two bronchial cartilages, which are infiltrated. A lymph node at the upper right shows no tumor metastasis. C Photomicrograph ( $\times 315$ ) showing the histology of the tumor cells and their stroma, and invasion of a bronchial cartilage on the right.

CASE 3.—G. M. (No. 243282), a white female, 62 years of age, was admitted to the hospital on June 14, 1940, complaining of a productive cough and weakness since an attack of pneumonia one and one-half years before admission. The patient gave a history of having had severe attacks of pneumonia sixteen years and nine years before admission. Following the second attack of pneumonia she had a non-productive hacking cough which changed very little in character until her third attack of pneumonia one and one-half years before admission. The third attack of pneumonia was bilateral. Following this, her cough became productive without a foul odor. She did not regain full health after that time, having lost about thirty five pounds in weight during the illness.

An x-ray film of the chest taken a year ago revealed a "shadow" in the right lower chest region which was interpreted as tuberculosis. However, the sputum was

negative for tubercle bacilli. Three months before admission a bronchoscopy was performed. A tumor found, located in the right lower lobe bronchus, was said to be a cancer. There was no history of hemoptysis or dyspnea. She had had a vague pain in the right chest for about a month and for the past six or seven months there was a history of vomiting on going to bed when attempting to lie on the right side. The remainder of the history was irrelevant.

Physical examination revealed a well-developed, fairly thin white female who did not appear acutely ill. Temperature 98.6°; pulse, 85. The abnormal findings were chiefly limited to the chest. Expansion was equal and normal. The patient coughed occasionally and this was slightly productive. Râles were present on the right side in the anterior axillary line over the lower lobe after coughing. Breath sounds and tactile fremitus were somewhat diminished over this area. There was just a suggestion of clubbing of the finger tips.



Fig. 3A.—Case 3. G. M. X-ray of chest on admission showing an opacity in the lower right lung field made by the atelectatic and infected right lower lung lobe.

*Laboratory Findings.*—The blood showed a hemoglobin of 87 per cent; R.B.C., 3,64; and W.B.C., 12,350. The Wassermann and Kahn tests were normal, as was also the urinalysis. An x-ray of the chest revealed a pyramidal-shaped opaque area occupying the right posterior costophrenic angle (Fig. 3A). The remainder of the lung fields were relatively normal. Diagnosis: atelectasis and pneumonitis of the right lower lobe due to bronchial obstruction, probably by tumor. The bronchoscopic examination revealed a tumor in the right lower lobe bronchus. It was a red, smooth, and rounded mass and on biopsy showed carcinoma of the bronchus. The patient was prepared for an operation by transfusion, and a right lower lobectomy by the dissection technique was performed.

The patient made an uneventful convalescence for the first ten days, the temperature returning to normal. As she was ready to be allowed out of bed, massive

infarction of the right middle lobe developed. She gradually developed signs of congestion and pneumonia with cardiac failure, and died twenty-six days after operation.

Post-mortem examination revealed pulmonary embolism with massive hemorrhagic infarction of the right middle lobe, terminal pneumonia, and a small encapsulated empyema.

*The Tumor and Right Lower Lobe.*—(Autopsy No. 5087; Prosector, Dr. Howard C. Hopps.) The surgical specimen of excised right lower lobe showed a tumor 3.5 by 2.0 by 1.5 cm. located in the primary and a secondary bronchus of the right lower lobe, to whose wall it was attached. It filled and dilated the bronchi in which it was located. The tumor on section was hard and white. Half of the lobe distal to the tumor showed bronchiectasis and the other half showed atelectasis. (Figs. 3B and 3C.) The lung lobe was heavy and practically airless. When cut across purulent material escaped from the bronchiectatic portion.



Fig. 3 B and C.—Case 3. B. Photograph of hilar surface of the excised lung showing the polypoid tumor projecting into the main bronchus. C. Photograph of a large microscopic section through the lung to show the tumor arising in a large bronchus, the bronchiectasis, and the atelectasis.

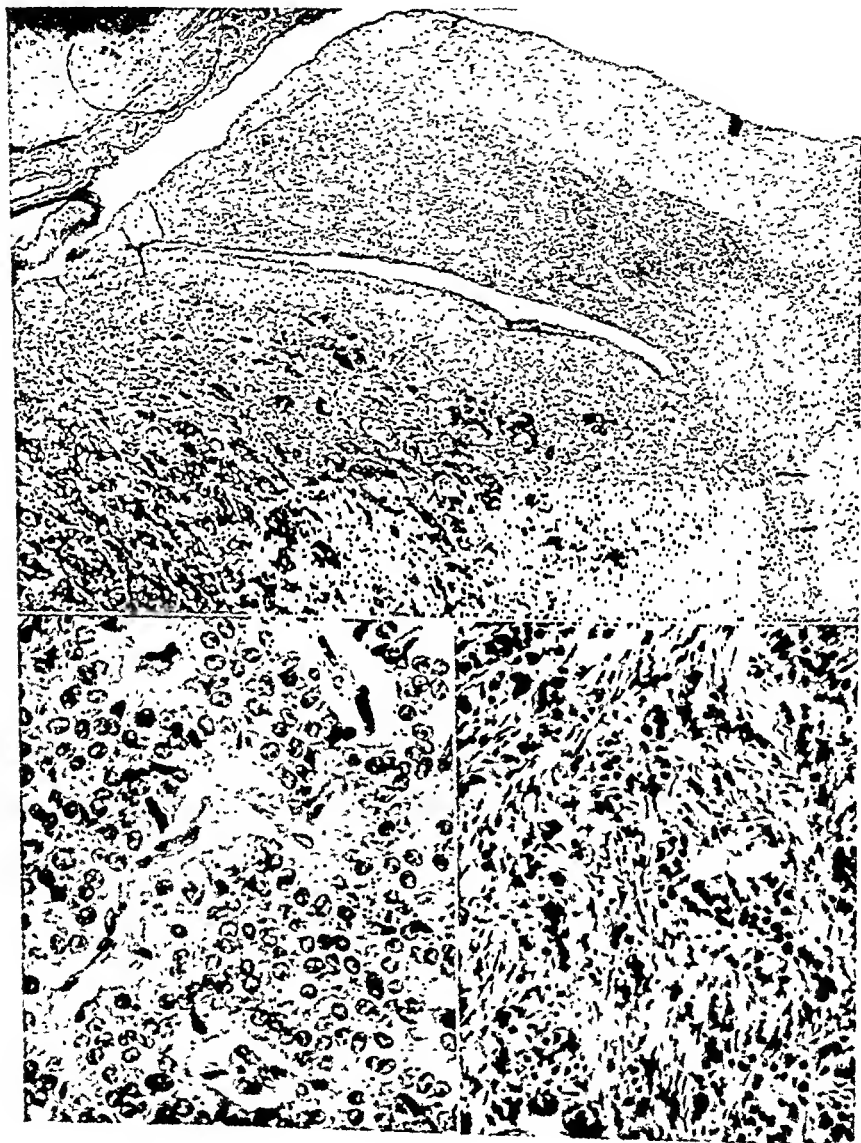
Microscopically the tumor was composed of fairly uniform polyhedral cells which grew in sheets or in several layers piled up on a uniform, vascular connective tissue framework. In some areas the cells were low columnar and they were arranged in a single layer on a distinct papillary stroma. The nuclei were uniform in size, oval, moderately hyperchromatic, and with the chromatin showing considerable clumping. Nucleoli were fairly large. Practically, there were no mitotic figures. The cytoplasm was moderately abundant, very finely granular, slightly acidophilic, and indistinct in outline. (Fig. 3E.)

The tumor arose from the bronchial wall. Beneath its pedicle, in bronchial lymphatic channels, nests of tumor cells were visible. At one point there was direct infiltration of tumor cells into bronchial cartilage.

The free surface of the tumor was capped by a layer of dense fibrous tissue. This in turn was covered, in the most advanced tip, by a layer of fibrin and hemorrhage. Elsewhere the tumor was covered by a stratified squamous epithelium, although the adjoining bronchial wall was lined by normal appearing pseudo-stratified columnar epithelium. (Fig. 3D.)

The bronchi distal to the point of obstruction by tumor showed a marked bronchiectasis. The lung parenchyma showed small areas of recent abscess formation. It also showed an atelectasis. The alveolar spaces contained blood which showed no degeneration.

*D.*



*E.*

*F.*

Fig. 3 *D*, *E*, and *F*.—Case 3. *D*. Photomicrograph ( $\times 27$ ) showing the intrabronchial tumor with its surface layer of fibrous tissue, stratified squamous epithelium, and at the upper right by a layer of fibrin infiltrated by leucocytes. *E*. Photomicrograph ( $\times 560$ ) showing the character of the tumor cells and their stroma. *F*. Photomicrograph ( $\times 200$ ) of vertebral body showing a tumor metastasis with more fibrous stroma and greater cell pleomorphism than in the primary bronchial tumor. This lesion was several centimeters in size and had completely replaced the marrow at this point.

In a routine section of bone taken from a lumbar vertebral body to study the condition of the bone marrow, microscopic examination disclosed a nodular, infiltrative lesion replacing the marrow cells in which the cells resembled those of the lung tumor. There was considerably more fibrous stroma than in the primary growth, and in some places the epithelial cells had died out altogether.

CASE 4.—J. D. (No. 30016), a white male, aged 47 years, was first admitted to the hospital on Nov. 19, 1930, complaining of tiredness for one year and attacks of paroxysmal coughing for one and one-half years. The patient gave a history of a severe attack of pneumonia in 1924. He went to Arizona to recuperate and remained quite well until a year before admission. However, during the years following the attack of pneumonia, he tired easily and was not up to par. For this reason his engagement in sports was given up. During the three months before admission the feeling of fatigue gradually increased and attacks of coughing became more severe. These were difficult to control. The sputum raised was fairly large in amount and quite thick and tenacious with no evidence of blood. On some occasions, on taking his own temperature, it was found to be increased by as much as one degree. The history was otherwise irrelevant.

Physical examination revealed a well-nourished and well-developed man who did not appear ill. His temperature was 99.4° and pulse 88. Examination in general was strikingly normal. His blood pressure was 130/90. His heart and lungs revealed no definite evidence of abnormality. There was no evidence of clubbing of the finger tips.

*Laboratory Examination:* His blood showed a hemoglobin of 85 per cent; R.B.C., 3.85; and W.B.C., 12,300. The Wassermann and Kahn tests were negative as was also the urine examination. The sputum on several examinations was negative for tubercle bacilli. An x-ray of the chest revealed a fairly sharply outlined shadow at the right hilum extending somewhat outward toward the periphery. It was considered most likely either a pulmonary neoplasm or an atypical hilum tuberculosis. The patient was observed in the hospital for a period of five weeks, at the end of which time he was quite comfortable and had had a normal temperature for over four weeks. During his stay in the hospital an investigation of the gastrointestinal tract was found to be normal. After a short time following his discharge, he returned to Arizona for a rest. His cough continued at intervals and the possibility of foreign body aspiration was considered. Bronchoscopic examination revealed the mucosa of the right primary bronchus to be intensely inflamed. There was an edematous bulge inward of the orifice of the right upper lobe bronchus. A tumor of this bronchus was suspected but microscopic sections revealed no definite mitotic figures. Because of the suspicion that the lesion was neoplastic in nature, x-ray therapy was considered advisable. From Nov. 2 to Nov. 16, 1931, he received 1,300 r. units and from January to October, 1932, he received an additional 5,131 r. units, making a total of 6,431 r. units. Following this, the patient was again seen in the Out-Patient Clinic from time to time and remained in fairly good condition until two weeks before his second admission to the hospital on Oct. 14, 1934. At that time he developed a head cold with chills and pains in the chest. An x-ray of the chest just before admission revealed no change from one taken four years previously. On the day prior to admission he developed a chill, felt flushed, became nauseated, and was brought to the hospital. His temperature was found to be 103.4°. Examination of his chest revealed little evidence of abnormality. His W.B.C. was 24,000; hemoglobin, 90 per cent; and R.B.C., 5.12. Examination of the sputum revealed a Type VIII pneumococcus. He rapidly became worse; definite signs of pneumonia developed, first on the right side and subsequently on the left. His temperature became elevated to 104.2° and the pulse 150. On the sixth day after entering the hospital he died of bilateral pneumonia.

*The Tumor and Lung.*—(Autopsy No. 3248; Prosector, Dr. Sion Holley.) A tumor cast filled both branches of the right upper lobe bronchus. The tumor tissue was soft, white to red, and fleshy. It dilated the bronchi, which were thin walled, and filled two of the main bronchi which passed toward the apex of the lung, as well as some of their branches. As felt externally through the lung tissue the overall size of the tumor was roughly 5 or 6 cm. On gross examination the tumor appeared to be confined within the lumens of the dilated bronchi. Two calcified or ossified bodies were found in the tumor of one bronchus.

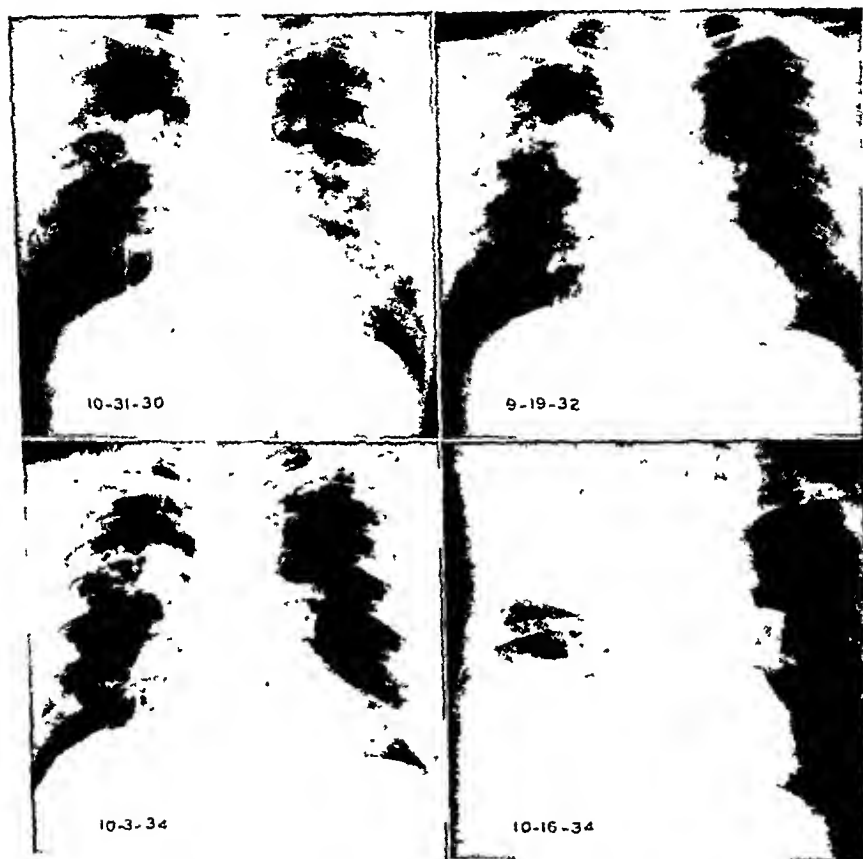


Fig. 1 A.—Case 4. T. D. Four x-rays of the chest over a four-year period. Note that the opacity made by the tumor in the right upper lobe remained practically unchanged during this time.

The bronchi distal to the tumor were dilated up to 12 mm. and were filled by a yellow to gray pus. The lung weighed 1,400 Gm. The upper lobe was consolidated and gray, the lower lobe was consolidated and was red gray. Two areas of beginning suppuration were found. The middle lobe showed only a bloody edema. The surface of the lung was covered by a fibrinopurulent exudate. The left lung weighed 1,150 Gm. It showed areas of red consolidation in the apex, lingula, and upper portion of the upper lobe, a diffuse hyperemia and edema elsewhere, mucopurulent bronchitis, and fibrinopurulent pleuritis.

Bacterial cultures from each lung, heart blood, and a bronchiectatic cavity in the right upper lobe all yielded a Type VIII pneumococcus.



Microscopically the tumor was composed of small, fairly uniform, euboidal to polyhedral epithelial cells. The nuclei were round to oval, hyperchromatic, fairly uniform in size and shape, and without mitotic figures. The cytoplasm was scanty, clear, poorly defined, and very slightly acidophilic. These cells grew in sheets but more commonly as a layer arranged on cords of connective tissue which was highly vascular but often hyalinized. (Fig. 4B.) The total effect was that of a semi-papillary tumor growth. This tumor permeated and filled the bronchial tree in the region of the right upper lobe as already indicated. Microscopic examination also disclosed, however, that the tumor was invading through bronchial walls in several places, and was growing in the adjacent alveoli. There was a remarkable tendency for the tumor growth to be coated by fibrous tissue, which was hyalinized, and for the bronchial walls themselves to become hyalinized even at points of tumor penetration.

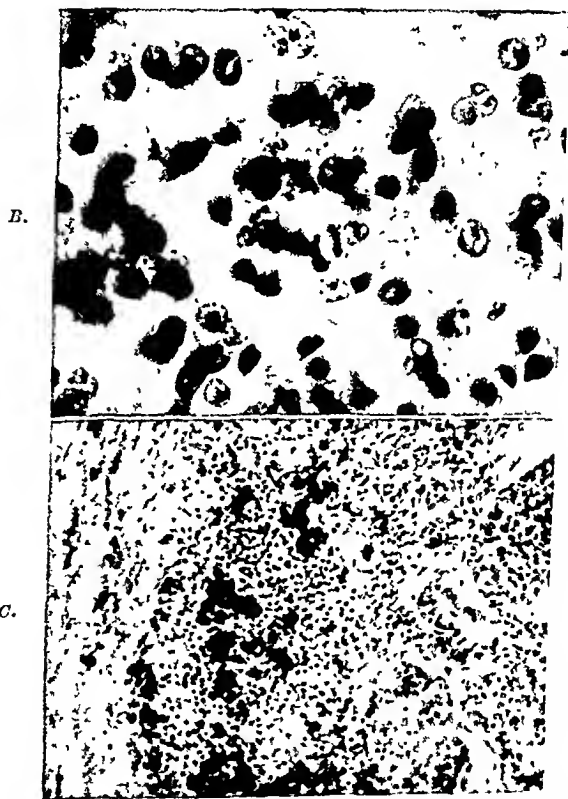


Fig. 4 B and C.—Case 1. B. Photomicrograph ( $\times 1170$ ) showing the histology of the tumor cells. C. Peribronchial lymph node ( $\times 330$ ) showing from left to right periglandular fat, lymph node capsule, lymphatic tissue with anthracotic pigment, and metastatic tumor growth.

A microscopic metastasis of the tumor was discovered in one peribronchial lymph node.

Apart from the tumor the sections of the lungs disclosed bronchiectatic cavities, apparently of recent origin, filled by purulent exudate in the right upper lobe distal to the points of occlusion by tumor, and a fibrin-rich lobar pneumonia which in some areas appeared to be of recent origin and elsewhere near the point of resolution, early areas of suppuration in the lung, and a pleuritis.

CASE 5.—M. G. (No. 235601), a white female, 36 years of age, was admitted to the hospital on Feb. 5, 1940, complaining of a draining sinus in the right chest for eleven years, a second draining sinus from the anterior aspect of the right chest for four years, marked loss in weight and strength and easy fatigability for three years. The patient gave a history of a severe attack of pneumonia fifteen years before admission. This was complicated by an empyema which was drained by a physician. This continued to drain for six months after which she felt well for a period of four years. Eleven years before admission the sear of the former operation became infected and was opened by a physician. Pus had drained from this site ever since (eleven years). About four years ago, the patient noticed a lump on the front of the right chest wall, just below the clavicle. This was incised and has drained pus since that time. The patient stated that she had lost twenty-five pounds in weight up to five years before admission and an additional twenty-seven pounds since that time. She had had chills and fever on various occasions and an occasional dry cough from time to time which had been rather insignificant and never productive. There was no history of hemoptysis. The remainder of the history was irrelevant.

Physical examination revealed an extremely emaciated anemic white female who appeared very exhausted and chronically ill. Her temperature was 100° and her pulse 120. The abnormal findings were as follows: The right chest was markedly contracted, producing a considerable degree of scoliosis of the spine. A draining sinus productive of foul, yellowish-green purulent material was seen just below the right scapula. A second sinus draining similar material was located immediately beneath the right clavicle. The entire right chest was flat on percussion, tactile fremitus was markedly diminished or absent, and no breath sounds could be heard. The left lung field was relatively normal. The heart borders were within normal limits and there were no murmurs. Clubbing of the fingers was quite marked. The extremities revealed marked wasting and the patient was unable to stand because of weakness.

*Laboratory Findings.*—The blood hemoglobin was 40 per cent; R.B.C., 3.42; and W.B.C., 7,150. The Wassermann and Kahn tests were negative, as was also the urine examination. An x-ray of the chest revealed a lack of aeration of the entire right lung with marked thickening of the pleura and a pyopneumothorax. The trachea was deviated to the right. The left lung was relatively normal. Diagnosis: chronic empyema, right.

The patient was given a blood transfusion in preparation for drainage of the empyema. A Congo red test showed only 15 per cent retention in the body. Open drainage of the empyema by rib resection (ninth and tenth) was carried out. Another blood transfusion was given and the patient made a gradual recovery, a third transfusion being given two weeks after operation. Considerable strength was regained and her temperature and pulse returned to normal. She was discharged from the hospital on the twenty-sixth day following operation, with a hemoglobin of 60 per cent; R.B.C., 4.52; and W.B.C., 7,350. The empyema cavity which measured 100 c.c. at operation had diminished to 70 c.c. at the time of discharge.

The patient was followed in the Out-Patient Clinic at weekly intervals. She gained rapidly in weight and strength and in two months had improved very remarkably. Her weight had been increased by 17 pounds; the cavity had been reduced to around 55 c.c.; the blood picture had improved to a hemoglobin of 76 per cent and R.B.C., 4.65. She was admitted on May 3, 1940, for obliteration of the remaining portion of her empyema cavity. On May 8, 1940, a first stage of a graded thoracoplasty was performed, portions of the second, third, fourth and fifth ribs being resected subperiosteally. The operation was well tolerated, little reaction being exhibited, and the temperature returned to normal on the first postoperative day. About one week later it was noticed that she exhibited a slight wheezing type of

respiration for the first time. A bronchoscopy was performed with dramatic findings. A tumor mass arising in the right main bronchial tree was seen projecting into the lower end of the trachea to such an extent that the carina was invisible and the left primary bronchus could not be seen. A biopsy removed gave the impression at first of a squamous-cell carcinoma. Edema and inflammation following the bronchoscopy caused considerable dyspnea. The bronchoscopy was repeated in an attempt to remove a sufficient amount of the tumor to obtain a clear airway to the left lung. This was again followed by marked dyspnea and during the third attempt at removal of the intratracheal portion of the tumor, the patient died, death being due to asphyxia.



Fig 5 A.—Case 5. M. G. X-ray of chest on admission. The right side is markedly shrunk and presents a chronic pyopneumothorax.

*The Tumor and Lungs.*—(Autopsy No. 5051; Prosecutor, Dr. W. M. Humphreys.) The right lung was small, airless, and solid. More than half of it was replaced by tumor tissue which centered in the greatly dilated bronchial system of the lower lobe, but which also extended into the right main bronchus, the proximal portions of the bronchi to the right upper and middle lobes, and into the trachea. The right main bronchus was filled by tumor and was dilated to twice its normal size. Proximally the tumor formed a polypoid mass which projected into the trachea for a distance of 2 cm. and partly obstructed its lumen. The proximal end of the left main bronchus wall was infiltrated by tumor. Distally the tumor formed a multilobulated mass, the different projections representing tumor growing as a cast in greatly dilated bronchi. Capping this multilobulated tumor, and filling the spaces between lobules was a layer of totally atelectatic, anthracotic lung tissue from 1 to 15 mm. thick. This in turn was covered by a greatly thickened, tough, fibrous pleura which was up to 2 cm. thick. The only pleural space which persisted consisted of two empyema cavities, one 5 cm. across and the other 6 cm., which communicated with each other and with lung abscesses, and drained to the exterior through sinus tracts, one spontaneous and the other operative.

Only near the central portion of the tumor mass was there any perceptible invasion through the bronchial wall into the lung parenchyma. The remarkable dilatation of the secondary bronchi by tumor could be followed nearly to the surface of the lung by the position of their cartilage rings, some of which were calcified or ossified. Tertiary bronchi were also enormously dilated up to 3 cm. and were filled by inspissated exudate. Some such cystic tertiary bronchi showed the blunt end of an advancing tumor polypus projecting into them. They lay near the pleural surface.



Fig. 5 B and C.—Case 5. B. Photograph of lower portion of right lung showing the tumor extending into the trachea. Although not well illustrated the massive growth is largely intrabronchial. C. Photomicrograph (X25) showing the nature of the intrabronchial tumor propagation, its fibrous cap covered by columnar epithelium but with focal metaplasia to stratified squamous epithelium. In the bronchial wall above is a spicule of bone. A lymph node at the upper left shows no tumor metastasis.

The right middle and upper lobes were atelectatic, contracted, firm, and anthracotic. The proximal ends of their large bronchi were filled by a cast of tumor

tissue which was continuous with the tumor in the right main bronchus. The tumor was attached here and there to the bronchial walls, and where not so attached its surface was smooth and pale.

The large arteries and veins of the lower lobe were firmly compressed but not visibly invaded by tumor. One right hilar lymph node showed direct invasion from contiguous tumor.

In general the tumor tissue was moderately firm and elastic, and was pinkish white.

The left lung showed a mucopurulent bronchitis, areas of atelectasis, and some irregular hyperemia and edema. In addition there was in the apex an area 2 by 1.5 by 1 cm. of fibroplastic and fibrocaseous tuberculosis with tuberculous bronchiectasis. Beneath this were several 5 mm. sized parenchymal tubercles. In the tracheobronchial lymph nodes were about a half-dozen well-encapsulated caseocalcareous tubercles from 3 to 5 mm. in diameter.

Microscopic examination revealed that the tumor was composed of small, uniform, polyhedral, cuboidal or low columnar cells, arranged occasionally in small sheets but usually in rows, single or several layers deep, on a fibrous stroma in a compact papillary form. Occasionally, also, there appeared to be small ducts or alveoli. The cells had a round or oval nucleus which was hyperchromatic with the chromatin showing little clumping. Mitotic figures were practically not to be found. The cytoplasm was scanty, clear, and very slightly acidophilic. There was no evidence of secretion. The stroma was widespread and in some places hyalinized. (Fig. 5E.)

This tumor formed a mass which propagated through the bronchial system, being adherent to the wall here and there. The intrabronchial tumor was capped in nearly all places by a layer of dense fibrous tissue, on which if epithelium was present it was generally stratified squamous. (Fig. 5C.)

The bronchi were dilated. Their epithelial lining was either replaced by granulation tissue, or it showed metaplasia to a stratified squamous type, or it less frequently remained pseudostratified columnar. The bronchial wall was frequently composed of dense fibrous tissue which was often hyalinized. Such bronchial walls were penetrated by tumor tissue only in the right lower lobe. The bronchial cartilages were separated. They sometimes showed invasion by tumor tissue. Frequently spicules of bone were found on or in close relation to bronchial cartilage, especially where perichondrium was infiltrated or elevated by tumor cells. (Fig. 5D.)

Except for operative sites and near the abscess cavity degenerative changes were not seen in the tumor.

There was no clue as to the exact point of origin of the tumor except that the greatest amount and degree of hyalinization of the stroma was near the center of the tumor in the lower lobe.

The lung parenchyma showed a remarkable chronic fibrosing pneumonitis, with foci of lymphocytes, fibrous tissue, and small endothelial-cell-lined alveoli. Lipophages and macrophages filled such alveoli.

The chronic empyema cavities and the subjacent superficial lung abscesses showed tuberculous granulation tissue with focal caseation and miliary epithelioid tubercles. This appeared to be a recent superinfection, and there was no indication that the generalized pleural fibrous thickening was tuberculous in origin. There was no tuberculosis elsewhere in this lung.

Microscopic examination of the left lung and of the tracheobronchial lymph nodes confirmed the diagnosis already given. One right hilar lymph node showed tumor growing within its substance but it appeared to have invaded directly from tumor adherent to its capsule. Other bronchial nodes, in close proximity to neoplasm, showed no metastases.

Metastases were not seen grossly or microscopically in numerous sections of other tissues except for two tiny microscopic groups of cells, in portal triads of the liver, which resembled the cells in the lung tumor.

Anatomical diagnosis: Carcinoma of the bronchus (malignant adenoma type) arising in the right lower lobe. Propagation of tumor through the bronchial tree, and focal invasion of lung parenchyma. Metastases to a right bronchial lymph node and to the liver (microscopic). Extensive chronic atelectasis, pneumonitis and bronchiectasis. Chronic empyema (tuberculous?).

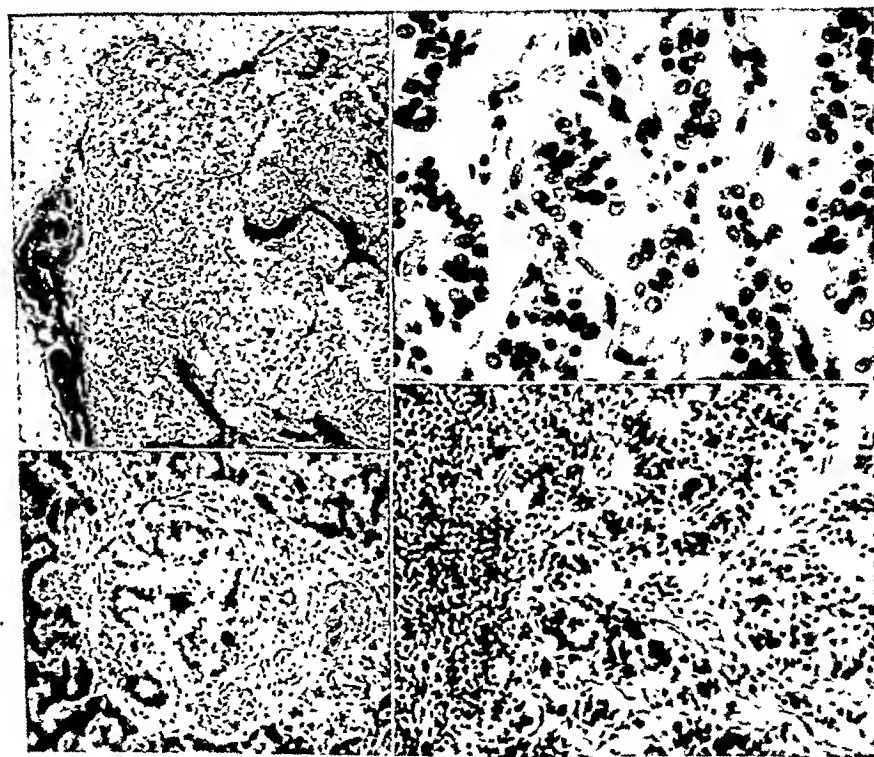


Fig. 5 D, E, F, and G.—Case 5. D. Photomicrograph ( $\times 58$ ) showing tumor invasion of bronchial cartilage with destruction and elevation of perichondrium, and spicules of bone. E. Photomicrograph ( $\times 575$ ) showing the nature of the tumor cells and their stroma. F. Photomicrograph ( $\times 165$ ) showing a growth of abnormal, hyperchromatic epithelial cells resembling those in the bronchial tumor, growing in a portal area which also contains two normal-appearing bile ducts. G. Photomicrograph ( $\times 220$ ) showing tumor in peribronchial lymph node.

#### DISCUSSION

A presentation of the clinical aspect of this type of tumor has been so thoroughly accomplished by Hamperl (1937),<sup>5</sup> Womach and Graham (1938),<sup>7</sup> Goldman (1940),<sup>8</sup> Brunn and Goldman (1940),<sup>9</sup> and others that only certain characteristics will be taken up in this discussion.

As seen in Table I, this tumor is as common in the female as in the male and occurs frequently in the third decade of life. These facts have been emphasized by most authors dealing with this subject. A

TABLE I  
CLINICAL DATA

CASE	AGE	SEX	HISTORY ON ADMISSION	DURATION	PHYSICAL AND LABORATORY FINDINGS	X-RAY	BRONCHOSCOPY
1. W. W.	33	F	Persistent cough with repeated "colds," 5 yr.; <i>pneumonia</i> 6 mo. ago with repeated serious <i>hemoptyses</i> since	5+ yr.	Thin, anemic, lower right chest flat and no B.S.; sputum, hemolytic streptococci; Hb., 47%	Atelectatic bronchiec-tatic right lower lobe	Tumor filling bronchus of right lower lobe
2. L. M.	37	M	Attacks of coughing, fever and sweats and <i>hemoptyses</i> during past 2 yr.; pleurisy, general malaise, weakness	3+ yr.	Lower left chest flat; B.S. > râles; sputum, hemolytic streptococci	Left lower lobe collapsed	Rounded tumor mass in left lower lobe bronchus; bled easily on section
3. G. M.	62	F	Chronic productive cough; weight loss 35 pounds during a period of 1½ yr.; <i>pneumonia</i> 1924, 1931, and 1938; dry cough since 1932	2-8 yr.	Chronically ill and anemic, weak; lower right lung field flat with coarse râles; R.B.C., 3.64	Collapse of right lower lobe	Tumor mass which bled easily located in right lower lobe bronchus
4. J. D.	47	M	<i>Pneumonia</i> with slow recovery, 1924; repeated colds and productive cough, fatigability and weakness since (6 yr.) cough increased; weight loss 16 pounds	4-10 yr.	First admission, not acutely ill; chest quite normal; R.B.C., 3.85; very little sputum, no blood Second admission, 4 yr. later; acutely ill; signs of bilateral <i>pneumonia</i> ; W.B.C., 34,000; pneumococcus Type VIII	First admission circumscribed shadow right upper lobe Second admission 4 yr. later same shadow as above, later obscured by pneumonia	In 1931 edematous bulging inward of origin of upper right lobe bronchus; microscopic section revealed tumor; no mitotic figures
5. M. G.	36	F	<i>Pneumonia</i> 15 yr. ago; empyema since then; slight cough; no hemoptysis or sputum; marked loss in weight and strength	15 yr.	Chronically ill; emaciated, anemic (Hb., 40%); rapid pulse; T, 100.8°; right chest shrunken; no B.S.; draining sinuses; clubbed fingers	Chronic empyema right with much shrinkage of chest wall; no aeration of right lung	Tumor almost completely filling lower end of trachea by extension from right main-stem bronchus

very noticeable clinical characteristic has been the repeated attacks of pneumonia over a period of several years. Recovery from these attacks has been the rule, a differential point between these and other more malignant lung carcinomata. Hemoptyses are frequently observed and are apt to be severe, the cause of which is easily explained by the pathologic characteristics. Other symptoms are variable and depend entirely on the basis of bronchial obstruction or infection of the lung subsequent to the obstruction. In some cases symptoms referable to the respiratory tract may be strikingly absent, even in the presence of a large tumor in a main stem bronchus.

Physical and x-ray findings are determined chiefly by the presence and extent of bronchial obstruction, lung infection, atelectasis, and other complications. A correct diagnosis can only be made following bronchoscopy with removal of adequate tissue for microscopic examination. Since all of these tumors arise in either the primary or secondary bronchi, they are readily visualized through the bronchoscope except when located in an upper lobe bronchus.

#### PATHOLOGY

An indication of the lack of universal opinion regarding the terminology of this lesion may be seen in the titles given by the following authors:

AUTHOR	DATE	TITLE
Geipel <sup>10</sup>	1931	Basal-cell cancer
Wessler and Robin <sup>11</sup>	1932	Benign bronchial adenoma
Kernan <sup>6</sup>	1935	Carcinoid
Moersch and Bowing <sup>12</sup>	1935	Adenocarcinoma
Clerf and Crawford <sup>13</sup>	1936	Benign glandular tumors
Zamora and Schuster <sup>14</sup>	1937	Vascular adenoma
Welt and Weinstein <sup>15</sup>	1937	Endothelioma
Hamperl <sup>18</sup>	1937	Cylindroma and carcinoide
Womach and Graham <sup>7</sup>	1938	Mixed tumors of the lung
Ochsner <sup>16</sup>	1940	Reserve-cell tumor
Goldman <sup>5</sup>	1940	Polypoid bronchial tumors

In all probability most of these authors have been describing the same type of tumor. A careful study of the five tumors in this report shows how some of the above titles may be justifiable.

The question arises as to what extent benign epithelial polypoid tumors of the bronchus can be separated from the slightly or ultimately malignant tumors. It is impossible at this time to determine if any bronchial polypoid tumor will remain continuously benign. To our knowledge no one has presented histologic criteria by which on biopsy it can be predicted how much of the tumor is within the bronchial lumen or to what extent direct invasion of the surrounding structures or distal spread of the tumor has taken place; furthermore,



TABLE II  
PATHOLOGY

CASE	SIZE	GROSS			MICROSCOPIC		
		LOCATION	SECONDARY CHANGES	CELL TYPE	LOCAL EXTENSION	METASTASIS	
1. W. W.	2 cm. diameter	Primary bronchus of right lower lobe	Bronchiectasis and atelectasis of entire lobe	Small deep staining cells with large nuclei; mitotic figures rare; cells arranged in cords and tend to form pseudocini; free portion in bronchus covered by squamous epithelium	Invasion of bronchial wall	None found at operation	
2. L. M.	2.2 by 1.4 by 1 cm.	Primary bronchus of left lower lobe	Bronchiectasis and atelectasis of entire lobe		Invasion of bronchial wall	None	
3. G. M.	3.5 by 2.0 by 1.5 cm.	Primary and secondary bronchi of right lower lobe	Bronchiectasis of one-half of lobe and atelectasis of other one-half		Invasion of bronchial wall	To bone marrow	
4. J. D.	6 cm. diameter	Primary and secondary bronchi of right upper lobe	Bronchiectasis of right upper lobe; pneumonia		Invasion of bronchial wall and to some extent the immediate surrounding parenchyma	To one tracheobronchial lymph node	
5. M. G.	7 by 10 by 8 cm.	Extended up into trachea and involved entire right lung, chiefly by extension along air passages	Chronic emphysema; obstruction of left primary bronchus		Invasion of walls of air passages and adjacent structures; spread along air passages	Mediastinal nodes adjacent to lung; liver	

whether distant metastases, such as those found in three of the cases presented here, will subsequently occur.

A summary of the pathologic findings of our cases follows:

Analysis of these 5 cases shows that in the early stages the tumors were polypoid, intrabronchial growths. Later the main growth was still intrabronchial, with tumor permeation of portions of the bronchial tree, but in addition there were areas in which the tumor grew deep into or through the bronchial wall. They occluded the bronchus and produced local enlargement. The lung distal to the occlusion showed bronchiectasis, infection, and atelectasis.

Microscopically the tumors showed only minor differences. They were composed of fairly uniform polyhedral, cuboidal or low columnar, undifferentiated epithelial cells, which were arranged on an abundant stroma. The stroma was fairly vascular, sometimes hyalinized, and was reticulated or papillary. The cells were arranged on the stroma in one or more cell layers. Mitotic figures were not seen. Necrosis was not present. There was no evidence of secretion by the cells, and they were not argentaffine in the three cases in which this examination was made.

The free surface of the tumor was covered by a cap of dense connective tissue into which tumor cells sometimes penetrated. This surface in turn, if not ulcerated, was covered usually by stratified squamous epithelium even if the adjacent bronchial wall had retained its normal pseudostratified columnar epithelium. Deposits of fibrin were found on the surface after trauma by biopsy. The tumor infiltrated the bronchus at its base. Here there was an increase in fibrous connective tissue also, but it was less perfect as a capsule than that on the free surface. The bronchial cartilages were eroded by tumor.

In 3 of these cases bone was found in the tumor. It was in relation to bronchial cartilage from which it apparently arose. There was no evidence that it was tumor bone. The cartilage in or near all the tumors was bronchial cartilage.

Tumor cells were found in regional lymph nodes in 2 cases; the possibility that this might represent direct invasion rather than metastasis was not excluded in Case 5. In 1 case true metastases were discovered in the liver on microscopic examination, and in another a metastasis was discovered in a lumbar vertebral body on routine microscopic examination of the bone marrow.

#### TREATMENT

The lack of universal opinion as to the correct form of therapy for this type of tumor is probably due chiefly to misinterpretation or insufficient knowledge of its various characteristics. Experience has already been of some value in this respect. For example, bronchoscopic removal frequently has been followed by recurrence of the

TABLE III  
THERAPY

CASE	BRONCHOSCOPIC REMOVAL	IRRADIATION	LOBECTOMY	PNEUMONECTOMY	RESULTS
1. W. W.	For biopsy only	--	Right lower 11/3/39	--	Returned to good health; no evidence of recurrence since operation on 11/3/39
2. L. M.	For biopsy only	--	--	First stage only	Died 2 wk. following operation of a fulminating empyema (left) and suppuration of left chest wall; hemolytic streptococci and other organisms
3. G. M.	For biopsy only	--	Right lower 6/27/40	--	Died 3 wk. after operation due to pulmonary embolism with infarction of right middle lobe, infection (pneumonia) and cardiac failure
4. J. P.	For biopsy only	Yes, Nov. '31 1300, R. U. Jan to Oct. 5131 R.U. <u>6431 R.U.</u>	--	--	Died (10/20/34) of bilateral pneumonia (pneumococcus Type VII) on sixth day after second admission and 4 yr. after first admission to hospital
5. M. G.	For removal of obstruction of left primary bronchus.	--	--	--	Empyema drained with marked improvement; expired of asphyxia on attempting bronchoscopic removal of intratracheal portion

tumor. Surgically removed lobes as well as autopsy specimens readily demonstrate why bronchoscopic removal may be not only difficult or impossible but also not without considerable risk. According to Brunn and Goldman,<sup>9</sup> Jackson and Konzelmann<sup>17</sup> and others, polypoid tumors of the bronchi may be either malignant or benign. Also, it has been amply demonstrated that bronchoscopic observation may not definitely determine which of the two types an individual tumor may be. Again, when a bronchial tumor projects into the lumen of the air passage, it is impossible to determine by bronchoscopic examination how much of the tumor is located outside of the bronchial wall. Thus, it seems reasonable to assume that bronchoscopic removal of bronchial tumors in general leaves much to be desired.

Until recent years surgical extirpation of lung tissue was attended by so great a risk that all lung tumors were treated either by bronchoscopic removal or by x-ray. After years of intensive investigation, treating hundreds of patients by this method, it has become generally believed and more recently quite definitely proved, that bronchogenic carcinoma has not been cured by x-ray therapy.<sup>1, 2, 18</sup>

With the development of a relatively safe technique for the removal of a lung lobe, an increasing number of lung tumors have been treated in this manner. Pneumonectomy has also made great strides in recent years. However, the risk attending the latter procedure is considerably higher than that attending the former. For this reason, it is obviously important to know which of the two operations should be used in this type of tumor. It is becoming more and more widely believed that the treatment should be based on the individual findings at the time of operation. When it appears likely that a lobectomy will remove adequately the tumor-bearing tissue, that is thought to be the operation of choice. When this is not possible a pneumonectomy should be performed.

As stated before, a great deal of confusion exists regarding the classification of the tumor under discussion. The marked variation in the microscopic appearance in different parts of the tumor is largely responsible for this lack of understanding. For this reason a small piece of tumor such as that taken through a bronchoscope for biopsy is apt to be very misleading in making a correct appraisal. Undoubtedly some reports of cures of highly malignant tumors by fulguration or x-ray may quite well have been on this basis.

Again, in order that statistics of surgical cures by excision may be more intelligently interpreted, sections should include the entire tumor for microscopic examination. It is only by this method of study that operative results may be evaluated according to the type of tumor involved.<sup>19</sup>

#### SUMMARY

A group of five cases of endobronchial tumor are reported which are characterized by a long clinical course with low-grade but very definite

malignant manifestations. Differentiation of benign from malignant epithelial tumors of the bronchi is not possible from bronchoscopic biopsy material alone since this offers no criteria as to the amount of tumor invading the surrounding structures or as to the presence of distal metastases. This is very strikingly demonstrated in a critical examination of the gross and microscopic material of the five cases reported. Treatment must be based on the assumption that these tumors are malignant or potentially malignant and should be removed by lobectomy or pneumonectomy. Because of the relative degree of risk associated with these operations, lobectomy should receive preference when it is sufficient for removal of the tumor-bearing tissue. In order that statistics of surgical cures of carcinoma of the lung may be more intelligently interpreted, sections for microscopic study should include the entire tumor. The group of tumors presented should not be confused with the highly malignant varieties.

## REFERENCES

1. Bloch, Robert G., and Bogardus, George: Bronchogenic Carcinoma, *Arch. Int. Med.* 66: 39-49, 1940.
2. Graham, E. A.: Primary Carcinoma of the Lung or Bronchus, *Ann. Surg.* 103: 1, 1936.
3. Simons, E. J.: Primary Carcinoma of the Lung, Chicago, 1937, The Year Book Publishers, Inc.
4. Overholt, Richard H.: Curability of Primary Carcinoma of the Lung, *Surg., Gynec. & Obst.* 70: 479, 1940.
5. Goldman, Alfred: Polypoid Bronchial Tumors, *California & West. Med.* 53: 123, 1940.
6. Kernan, John D.: Treatment of a Series of So-Called Carcinoid Tumors of the Bronchi by Diathermy, *Ann. Otol., Rhin. & Laryngol.* 44: 1167, 1935.
7. Womach, N. A., and Graham, E. A.: Mixed Tumors of the Lung, *Arch. Path.* 26: 165, 1938.
8. Hamperl, H.: Ueber gutartige Bronchialtumoren (Cylindrome und Carcinoides) *Virehows Arch. f. path. Anat.* 300: 46, 1937.
9. Brunn, Harold, and Goldman, Alfred: The Differentiation of Benign From Malignant Polypoid Bronchial Tumors, *Surg., Gynec. & Obst.* 71: 763, 1940.
10. Geipel, P.: Zur Kenntnis der gutartigen Bronchialtumoren, *Frankfurt. Ztschr. f. Path.* 42: 516, 1931.
11. Wessler, H., and Robin, C. B.: Benign Tumors of the Bronchus, *Am. J. M. S.* 183: 164-180, 1932.
12. Moersch, H. J., and Bowing, H. H.: Primary Carcinoma of the Bronchus Treated Successfully With Surgical Diathermy, *Ann. Surg.* 102: 989, 1935.
13. Clerf, Louis, and Crawford, Baxter, L.: Benign Glandular Tumors of the Bronchus, *Tr. Coll. Physicians of Philadelphia (series 4)* 4: 6, 1936.
14. Zamora, A. M., and Schuster, N.: Vascular Adenoma of the Bronchus, *J. Laryngol. & Otol.* 52: 337-343, 1937.
15. Welt, Bernard, and Weinstein, Samuel: Trio of Rare Bronchoscopic Cases, *Laryngoscope* 47: 30-49, 1937.
16. Ochsner, A.: Carcinoma of the Lung, Read at Third International Cancer Congress, Atlantic City, 1939.
17. Jackson, Chevalier L., and Konzelmann, Frank W.: Bronchoscopic Aspects of Bronchial Tumors, *J. Thoracic Surg.* 6: 312, 1937.
18. Steiner, Paul E.: Effects of Roentgen Therapy on Histologic Picture and on Survival in Cases of Primary Carcinoma of the Lung, *Arch. Int. Med.* 66: 140-151, 1940.
19. Churchill, Edward D.: Thoracic Surgery, *New England J. Med.* 220: 498, 1939.
20. Rienhoff, William F., Jr.: Graded Pneumonectomy in the Treatment of Tumors of the Lungs, *Bull. Johns Hopkins Hosp.* 64: 167, 1939.

## EXPERIMENTAL ATELECTASIS IN DOGS

ITS EFFECT ON PLASMA VOLUME, HEMOGLOBIN, HEMATOCRIT, BLOOD GASES, CIRCULATION TIME, AND PULMONARY BLOOD FLOW

JOHN L. KEELEY, M.D., AND JOHN G. GIBSON, II, M.D., BOSTON, MASS.  
(From the Laboratory for Surgical Research, and the Department of Medicine,  
Harvard Medical School)

AT PRESENT there is ample evidence to show that when lung tissue becomes atelectatic, the amount of blood it contains, the quantity of blood which passes through it per unit of time, and the rate of blood flow through it are all decreased.<sup>1-9</sup> It has also been shown that following the production of atelectasis there is a decrease in oxygen content and an increase in carbon-dioxide content of peripheral arterial and venous blood for a variable period of time.<sup>2</sup> Since many of these points have been shown in separate and in either acute or short-term experiments, the following study of experimental atelectasis was undertaken in order to correlate the findings in the blood gases, circulation time, hemoglobin, hematocrit, and in the proportion of the cardiac output passing through the atelectatic lung and to determine the total plasma volume in relation to the duration of atelectasis over a relatively long period of time.

### METHODS

The oxygen and carbon-dioxide content of arterial and venous blood were determined by the gasometric method of Van Slyke and Neill.<sup>10\*</sup> The hemoglobin concentration was determined by the photoelectrometric method of Evelyn.<sup>11</sup> The plasma volume (using the direct dye method) and the hematocrit readings were determined as described by Gibson and Evans.<sup>12</sup> The circulation time was determined by a modification of the method of Loevenhart, Schlomovitz, and Seybold,<sup>13</sup> 0.2 to 0.3 c.c. of a 0.5 per cent solution of sodium cyanide being injected into the right small saphenous vein in one series of observations, and into the right and left branches of the pulmonary artery in another series. A stop watch was used for timing the interval between the injection and the marked transitory increase in respiratory effort which constitutes the endpoint.

### MATERIALS AND EXPERIMENTAL PROCEDURE

Young growing normal male and female mongrel dogs weighing from 8.8 to 27.2 kg. were used. Basal studies of plasma volume, blood gases, hematocrit, and circulation time were made one to eight days prior to division and closure of the left bronchus. Anesthesia was induced by the intravenous injection of sodium pentobarbital (nembutal) in doses

\*In this part of the work we were assisted by the determinations of Dr. M. Pijean  
Received for publication, Aug. 25, 1941

of 32.5 mg. per kilogram of body weight. The left fifth rib was resected subperiosteally under aseptic technique and the chest was opened. At this point, intermittent insufflation through an endotracheal catheter was instituted. The respirator was adjusted so that the carbon-dioxide content of the blood was maintained at a level just below that which caused spontaneous respiratory movements. The pleura over the left bronchus was incised and the bronchus was carefully isolated by blunt dissection and with minimal disturbance to the arterial and venous channels of the lung. The bronchus was then divided between hemostats by a scalpel, and the ends were treated with phenol and alcohol. In an attempt to avoid contamination by intratracheal and intrabronchial organisms, the insufflation was discontinued while the proximal stump was being inverted.<sup>14</sup> The ends were closed by inversion without ligation by means of purse-string sutures of silk, care being taken to avoid passing the needle into the lumen of the bronchus. Mattress sutures of fine twisted silk were used to reinforce the purse-string closure. At this time areas of discoloration indicating atelectasis were seen throughout the left lung. Closure of the wound was accomplished by a series of closely placed mattress sutures of fine silk in the posterior periosteum and pleura. Just before closure of the layers was completed, the right lung was inflated to minimize the possibility of pneumothorax. Pericostal sutures encircling the fourth and sixth ribs served to relieve tension on the wound. The remainder of the wound was closed by interrupted sutures of fine silk.

Persistence of the atelectasis was established beyond doubt by the division of the bronchus, by roentgenographs taken at intervals during the experimental period (Fig. 1), and by the demonstration of complete atelectasis at subsequent operation and autopsy. After the operation, the animals were kept in standard dog kennels on a well-balanced diet and were turned out of their cages daily for spontaneous exercise and activities.

Subsequent studies may be divided conveniently into three groups; in the first, determinations of total plasma volume, hemoglobin, hematocrit, blood gases, and circulation time were made within 6 to 33 days after the closure of the bronchus and at comparable intervals during the remainder of the experimental period.

The second group of studies was made after atelectasis had been present for periods varying from 58 to 198 days and consisted of determinations of oxygen and carbon-dioxide content of the peripheral arterial and venous blood immediately before and immediately after the inhalation of pure oxygen for a period of ten minutes.

The third series of studies was done within a few days after the second series and consisted of the following procedure: Under anes-

thesia as described for the bronchial division and closure, bilateral thoracotomy was performed. The animals were then placed so that the anterior-posterior diameter of the chest was vertical. Samples of blood from (1) the left ventricle, (2) the pulmonary artery, (3) a right pulmonary vein (aerated lung), and (4) a left pulmonary vein (collapsed lung) were obtained, and their oxygen and carbon-dioxide content was determined. While the samples were being withdrawn from the pulmonary veins, a bulldog clamp was placed on the vessels proximal to the site of the puncture to prevent aspiration of blood from the left auricle. The samples were obtained within as short a period of time as



Fig. 1.—Roentgenogram taken one month after the production of atelectasis in Dog 1. The mediastinum is shifted to the left and the left half of the diaphragm is elevated.

possible; not more than five minutes elapsed between the withdrawal of the first and last (fourth) samples. With one exception (Dog 4), no change was made in the rate or amplitude of the impulses from the respirator or in the position of the animal during the withdrawal of samples. All samples except those from the right pulmonary veins were obtained through the left thoracotomy wound. Particular effort was made to minimize mechanical collapse of the aerated lung. After the blood samples had been collected, the circulation time through the aerated



of 32.5 mg. per kilogram of body weight. The left fifth rib was resected subperiosteally under aseptic technique and the chest was opened. At this point, intermittent insufflation through an endotracheal catheter was instituted. The respirator was adjusted so that the carbon-dioxide content of the blood was maintained at a level just below that which caused spontaneous respiratory movements. The pleura over the left bronchus was incised and the bronchus was carefully isolated by blunt dissection and with minimal disturbance to the arterial and venous channels of the lung. The bronchus was then divided between hemostats by a scalpel, and the ends were treated with phenol and alcohol. In an attempt to avoid contamination by intratracheal and intrabronchial organisms, the insufflation was discontinued while the proximal stump was being inverted.<sup>14</sup> The ends were closed by inversion without ligation by means of purse-string sutures of silk, care being taken to avoid passing the needle into the lumen of the bronchus. Mattress sutures of fine twisted silk were used to reinforce the purse-string closure. At this time areas of discoloration indicating atelectasis were seen throughout the left lung. Closure of the wound was accomplished by a series of closely placed mattress sutures of fine silk in the posterior periosteum and pleura. Just before closure of the layers was completed, the right lung was inflated to minimize the possibility of pneumothorax. Pericostal sutures encircling the fourth and sixth ribs served to relieve tension on the wound. The remainder of the wound was closed by interrupted sutures of fine silk.

Persistence of the atelectasis was established beyond doubt by the division of the bronchus, by roentgenographs taken at intervals during the experimental period (Fig. 1), and by the demonstration of complete atelectasis at subsequent operation and autopsy. After the operation, the animals were kept in standard dog kennels on a well-balanced diet and were turned out of their cages daily for spontaneous exercise and activities.

Subsequent studies may be divided conveniently into three groups; in the first, determinations of total plasma volume, hemoglobin, hematocrit, blood gases, and circulation time were made within 6 to 33 days after the closure of the bronchus and at comparable intervals during the remainder of the experimental period.

The second group of studies was made after atelectasis had been present for periods varying from 58 to 198 days and consisted of determinations of oxygen and carbon-dioxide content of the peripheral arterial and venous blood immediately before and immediately after the inhalation of pure oxygen for a period of ten minutes.

The third series of studies was done within a few days after the second series and consisted of the following procedure: Under anes-

Dog 1	15	13.1	15.5	36.7	50.2	11.6	16.9	86.0	37.4	14.1	70.0	39.7	10
	15	13.1	320	38.8	51.7	11.0	11.8	81.0	37.7				8
	18	15.7	628	40.0	51.9	16.0	18.7	82.0	33.3	13.8	60.0	37.5	10
	97	17.0	665	39.0	53.2	16.2	20.1	89.7	35.2	16.5	75.0	42.7	8
	116	18.7	782	11.8	52.3	16.0	20.1	89.0	35.0	16.5	72.0	42.0	8
	183	17.1	718	13.0	53.2	15.1	19.5	96.0	45.1	15.0	73.0	49.5	10
Dog 3	11	11.1	565	19.5	42.6	13.9	15.2	82.0	44.7	11.9	64.0	48.6	10
	11	11.9	518	46.0	13.7	10.1	11.7	84.0	36.9	6.8	48.0	43.5	11
	17	10.6	606	57.0	13.3	13.7	16.6	90.0	35.8	10.5	57.0	38.8	10
	82	11.9	652	51.7	14.8	13.7	17.3	91.0	35.7	13.7	74.0	41.0	9
	110	13.2	702	33.0	16.0	13.0	17.3	94.0	35.0	13.7	74.0	39.2	9
	138	13.9	720	51.8	42.9	13.7	17.3	91.0	35.2	13.0	70.0	39.2	9.5
	187	13.8	756	51.7	18.0	11.2	18.5	97.0	40.0	14.2	74.0	44.6	11
Dog 6	33	8.8	350	10.0	50.9	15.0	18.11	90.0	44.5	14.9	73.0	43.6	9.5
	33	8.2	352	10.0	53.3	12.1	16.0	91.0	17.0	12.1	69.0	49.8	7
	75	7.1	408	55.0	51.2	16.0	19.4	90.0	34.5	14.5	67.0	37.0	7
	96	9.6	369	10.0	55.5	17.7	20.7	87.2	35.2	15.7	61.0	45.0	8
	135	8.8	429	18.7	17.3	17.0	20.9	87.9	35.6	15.9	69.0	41.0	8
	182	9.0	485	51.0	19.0	14.4	17.9	93.0	41.5	14.8	70.0	40.0	9
Dog 7	6	22.7	1003	11.1	53.7	19.8	24.2	91.1	39.0	21.1	84.0	43.4	11
	6	21.1	1018	19.9	52.2	13.7		88.4		15.3	83.0	41.5	9
	18	23.1	938	10.0	57.9	13.7	16.4	89.4	39.0	15.3	83.0	43.2	11
	97	25.7	1017	10.7	57.0	13.6	17.1	96.0	41.0	15.2	83.0	47.7	11
Dog 9	9	11.6	727	19.9	52.3	18.4	17.8	82.4	44.0	15.3	62.0	45.2	11
	9	13.1	573	13.8	50.3	18.4	20.9	84.8	44.0	15.6	63.0	45.2	10
	58	15.0	560	36.0	56.0	16.1	21.2	98.0	45.2	13.7	62.6	50.0	11

TABLE I

WEIGHT, TOTAL AND UNIT VOLUME OF PLASMA, HEMATOCHIT, HEMOGLOBIN, CARBON-DIOXIDE AND OXYGEN CONTENT, OXYGEN CAPACITY, AND OXYGEN SATURATION OF ARTERIAL BLOOD; OXYGEN CONTENT AND SATURATION, CARBON-DIOXIDE CONTENT OF VENOUS BLOOD; AND LFG TO CAROTID SINUS CIRCULATION TIME IN DOGS BEFORE AND AFTER PRODUCTION OF EXPERIMENTAL ATELECTASIS

	POSTOPERATIVE INTER-VAL IN DAYS	WEIGHT IN KG.	PLASMA VOLUME		HEMATO-CRIT	HGB. IN GM. PER CENT	BLOOD GASES				CIRCULATION TIME IN SECONDS		
			TOTAL IN C.C.	C.C. PER KG.			ARTERIAL		VENOUS				
							O <sub>2</sub> CONTENT	O <sub>2</sub> SATURATION	CO <sub>2</sub>	O <sub>2</sub> CONTENT		O <sub>2</sub> SATURATION	CO <sub>2</sub>
Dog 1	*	11.0	464	42.0	51.9	15.3	17.5	85.0	40.8	11.0	53.0	14.0	11
	6	10.4	508	48.0	43.2	13.8	14.8	80.0	46.0	9.0	48.0	19.8	9
	34	11.7			58.0	14.7							7.5
	45	10.9	430	40.0	56.7	14.7							9
	85	10.4	476	44.7	56.7	19.3	22.2	85.6	41.88	15.2	58.0	15.2	8
Dog 2	112	11.6	495	42.7	54.7	16.7	21.7	92.0	38.5	15.4	66.0	13.5	8.5
	140	11.9	513	43.1	54.3	19.3	22.3	88.0	42.0	15.3	59.0	45.0	9
	*	10.9	642	59.0	37.6	12.1	15.0	92.0	36.0	10.1	62.0	40.0	13
	7	10.3	611	59.3	39.2	12.3	14.6	88.0	41.0	9.0	51.0	18.0	7
	15	10.2	537	52.6	44.0	12.8	14.7	86.0	42.0	10.0	57.0	18.0	
Dog 3	41	11.2	550	54.0	43.7	15.3							
	78	9.0	613	68.0	42.1	13.2	16.9	95.6	35.4	11.5	64.0	39.3	12
	105	9.5	623	65.0	40.1	12.8	16.4	96.0	32.0	11.3	63.0	39.6	10
	145	10.4	698	67.0	42.1	13.0	16.3	95.6	31.8	10.8	61.0	39.7	9.5
	198	12.0	671	56.0	43.0	14.9	17.6	88.0	37.8	10.7	63.0	39.2	10
Dog 3	*	13.6	550	40.4	51.7	14.5	16.0	82.5	41.0	12.7	63.0	13.0	11
	7	12.2	595	40.9	42.1	14.5	16.0	82.5	41.0	9.8	50.0	17.0	10
	33	12.8	550	43.0	47.0	13.9	14.8	79.0	42.0	9.0	48.0	18.0	12
	61	13.4	438	32.0	54.1	13.1	14.9	84.0	45.0	10.9	60.0	17.6	8
	103	13.9	543	39.0	52.4	17.0	22.2	97.5	36.0	15.0	65.0	14.6	12
Dog 3	131	13.7	511	37.3	53.2	17.9	20.1	83.7	42.0	13.2	55.0	19.7	9
	153	14.2	555	39.0	50.4	17.9	20.2	84.0	12.0	13.3	55.0	49.5	9
						14.8	17.6	89.0	38.0	11.3	70.0	15.0	11

\*Preoperative basal levels.

\*Preoperative basal levels.

examined six or more days after atelectasis had been produced. In two animals there were slight increases at that time. In only one of the six animals did the decreases persist during the second month of atelectasis. In the other five animals which showed early decreases in circulation time these decreases disappeared during the second month and returned thereafter, only to disappear again after the fourth month of atelectasis (Fig. 2). It has been shown in acute experiments that when one lung is rendered atelectatic the increase in the proportion of the cardiac output which passes through the aerated lung is accompanied by a decrease in circulation time through the aerated lung.

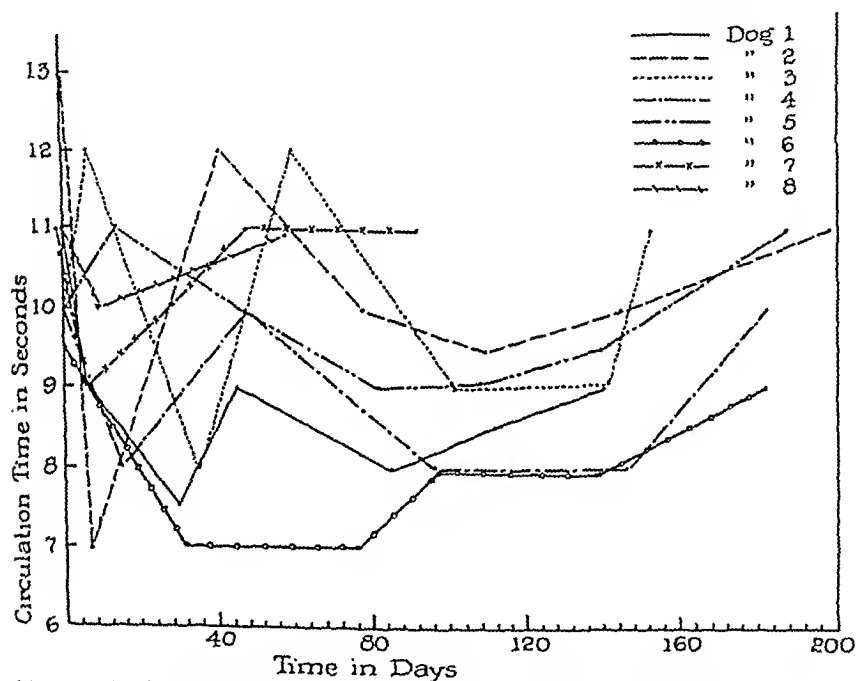


Fig. 2.—Circulation time from a leg vein to the carotid sinus as measured by the cyanide method in relation to the duration of atelectasis.

The effects of inhalation of pure oxygen for a period of ten minutes after from 58 to 198 days of atelectasis are presented in Table II. There followed in all animals, an increase in oxygen content of arterial blood which averaged 0.8 volumes per cent, or an increase of 2.3 per cent. In four of the seven animals there was a slight decrease in carbon-dioxide content of arterial blood which averaged 0.9 volumes per cent, or -0.46 per cent. Similar results were seen in the venous blood. The oxygen saturation of arterial blood was increased 4.4 per cent, while that of the venous blood was increased 4.0 per cent. These findings indicate that the degree of oxygen unsaturation found in the peripheral blood after many months of atelectasis is not entirely due to the admixture of arterial

and the atelectatic lung was determined by the injection of sodium cyanide into the right and left branches of the pulmonary artery, as described in detail elsewhere.<sup>7</sup> Just before closure of the second thoracotomy wound was completed, the aerated lung was inflated in an effort to minimize the possibility of pneumothorax. Seven to ten days later, the animals were sacrificed and appropriate studies of the tissues were made.

### RESULTS

The results in the first group of experiments are shown in Table I. The variable changes in the unit volume (cubic centimeters per kilogram) of plasma, with the exception of three determinations in Dog 2, are within the range of normal volumes for intact dogs<sup>15</sup> and therefore cannot be regarded as significant. Both the hemoglobin and the hematocrit values were increased in four of the eight animals. Because these increases were associated with increases in weight they cannot be considered a result of the atelectasis, as it has been shown that there is a general tendency for increases in weight to be accompanied by increasing values for hematocrit and hemoglobin.<sup>15</sup> This is thought to be due to the increase in the proportion of muscle, a blood-rich tissue, in normal growing dogs.

In most instances there was a decrease in the oxygen content and an increase in the carbon-dioxide content of both arterial and venous blood following the production of atelectasis. After the production of atelectasis the oxygen content of peripheral arterial blood was found to be reduced in seven of the eight animals. The reduction varied from 2 to 29 per cent of the basal value. In Dogs 1, 2, 3, and 6 there was a concomitant rise in the carbon-dioxide content of the arterial blood ranging from 2 to 13 per cent above basal levels. Oxygen saturation was decreased in Animals 1, 2, 3, 4, and 7 in determinations made within a week after atelectasis began. In Dog 6 there was a slight increase in the oxygen saturation but this determination was made thirty-three days after bronchial division and closure. At that time in the postoperative course the oxygen saturation was probably increasing, as is seen in the figures for Dogs 3 and 5. The increase in oxygen saturation in Dog 8 is probably an artifact, as the initial saturation of 72.4 per cent is so low as to indicate a false value for this determination. Decrease in the oxygen content and the oxygen saturation and increase in the carbon-dioxide content of venous blood were seen in Dogs 1, 2, 3, and 6. In Dog 5 the decrease in oxygen content and saturation was accompanied by a decrease in the carbon-dioxide content. Carbon-dioxide and oxygen content were both decreased in Dog 7 while the oxygen saturation remained essentially unchanged.

Circulation time from the saphenous vein to the carotid sinus was found to be decreased in six of the eight animals when they were first

and venous blood in the left auricle but depends to some extent on incomplete oxygen saturation of the blood passing through the aerated lung.

The third series of experiments yielded the results shown in Table III. Six animals had uneventful recoveries from the bilateral thoracotomy, one died on the operating table, and one died from postoperative sepsis. In two of the experiments the results were discarded because in one instance the heart action was failing while the blood samples were being withdrawn and in the other, due to deficient aeration, it was necessary to alter the rate of the respirator during the withdrawal of samples.

TABLE III

HEMOGLOBIN, CARBON-DIOXIDE, AND OXYGEN CONTENT, OXYGEN CAPACITY AND OXYGEN SATURATION OF BLOOD SAMPLES FROM (1) PULMONARY ARTERY, (2) RIGHT PULMONARY VEIN, (3) LEFT PULMONARY VEIN, AND (4) LEFT VENTRICLE IN RELATION TO DURATION OF ATELECTASIS, AND PROPORTION OF CARDIAC OUTPUT PASSING THROUGH ATELECTATIC LUNG

DURATION OF ATELECTASIS	DOG 1 142 DAYS	DOG 2 203 DAYS	DOG 3 159 DAYS	DOG 5 191 DAYS	DOG 7 106 DAYS	DOG 8 62 DAYS	AVER- AGE
Pulmonary artery (1)							
Hemoglobin	16.06	15.9	15.4	14.7	13.55	14.4	
Carbon dioxide	41.6	45.2	42.3		49.2		
Oxygen	16.7	14.82	15.44	14.00	10.8	10.8	
Oxygen capacity	21.52	21.3	20.6	19.7	18.2	18.90	
Oxygen saturation	79.3%	69.5%	75.0%	71.0%	59.4%	67.2%	70.2%
Pulmonary vein from right (aerated) lung (2)							
Hemoglobin	16.06	15.75	15.4	14.75	13.55	14.15	
Carbon dioxide	28.1	42.0	35.2		44.0		
Oxygen	21.5	18.6	20.0	19.15	16.35	17.05	
Oxygen capacity	21.52	21.15	20.6	19.8	18.2	18.95	
Oxygen saturation	99.5%	88.0%	97.0%	97.0%	90.0%	90.0%	93.6%
Pulmonary vein from left (atelectatic) lung (3)							
Hemoglobin	16.06	15.52	15.6	14.62	13.65	14.19	
Carbon dioxide	41.0	45.2	46.3		50.0		
Oxygen	15.25	14.1	15.45	14.25	10.7	12.5	
Oxygen capacity	21.52	20.8	20.9	19.6	18.3	19.0	
Oxygen saturation	77.0%	68.0%	74.0%	72.0%	59.4%	65.8%	69.3%
Left ventricle (4)							
Hemoglobin	16.4	15.52	15.4	14.75	13.55	14.4	
Carbon dioxide	30.2	42.6	36.0		45.1		
Oxygen	21.3	17.22	19.15	19.1	16.45	16.0	
Oxygen capacity	22.0	20.8	20.6	19.8	18.2	18.90	
Oxygen saturation	97.0%	83.0%	93.0%	96.4%	90.02%	85.0%	90.7%
Proportion of cardiac out- put through atelectatic lung	6.6%	25.0%	17.3%	2.4%	22.1%	20.6%	15.6%

As expected, oxygen content and saturation were highest in the blood from the aerated lung. The saturation in these samples varied from 88 to 99.5 per cent, with an average of 93.6 per cent. The lowest values for oxygen content and saturation were, of course, in the samples from the pulmonary artery and a left pulmonary vein (collapsed lung).

TABLE II

HEMOGLOBIN, CARBON-DIOXIDE AND OXYGEN CONTENT, OXYGEN CAPACITY AND OXYGEN SATURATION OF ARTERIAL BLOOD AND OXYGEN AND CARBON-DIOXIDE CONTENT AND OXYGEN SATURATION OF VENOUS BLOOD BEFORE AND AFTER INHALATION OF PURE OXYGEN FOR PERIOD OF TEN MINUTES

	HEMO- GLOBIN IN GM.	ARTERIAL CO <sub>2</sub> CONTENT	ARTERIAL O <sub>2</sub> CONTENT	ARTERIAL O <sub>2</sub> CAPACITY	ARTERIAL O <sub>2</sub> SATURATION %	VENOUS CO <sub>2</sub> CONTENT	VENOUS O <sub>2</sub> CONTENT	VENOUS O <sub>2</sub> SATURATION %	DURATION OF ATELEC- TASIS
Experiment 194, 4/9/37	14.92	37.8	17.6	20.0	88.0	43.0	12.7	63.5	198 days
Before breathing pure oxygen	15.0	35.5	19.8	20.1	98.5	41.9	14.7	70.0	
After breathing pure oxygen for 10 min.									
Experiment 200, 4/9/37	14.85	38.6	17.65	19.9	89.0	45.0	14.3	71.4	153 days
Before breathing pure oxygen	14.85	36.6	19.05	19.92	93.8	44.0	14.65	73.5	
After breathing pure oxygen for 10 min.									
Experiment 208, 4/21/37	15.15	45.1	19.5	20.3	96.0	49.5	15.0	73.9	183 days
Before breathing pure oxygen	15.15	43.9	19.8	20.3	97.5	49.0	15.25	74.8	
After breathing pure oxygen for 10 min.									
Experiment 209, 4/26/37	14.25	40.0	18.55	19.1	97.0	44.6	14.24	74.5	187 days
Before breathing pure oxygen	14.25	39.6	19.0	19.1	99.4	43.7	14.65	76.6	
After breathing pure oxygen for 10 min.									
Experiment 210, 4/21/37	14.45	41.5	17.9	19.35	93.0	50.0	14.8	73.2	182 days
Before breathing pure oxygen	14.45	41.4	18.6	19.35	96.0	49.0	16.15	83.0	
After breathing pure oxygen for 10 min.									
Experiment 230, 4/26/37	13.6	41.0	17.15	18.2	94.0	47.7	15.2	83.5	97 days
Before breathing pure oxygen	13.6	40.9	17.45	18.2	96.0	47.7	16.15	88.7	
After breathing pure oxygen for 10 min.									
Experiment 236, 5/3/37	16.1	45.2	21.2	21.65	98.0	50.0	13.75	63.5	58 days
Before breathing pure oxygen	16.1	45.2	21.32	21.65	98.5	49.5	13.99	64.6	
Average values before inhalation of O <sub>2</sub>	--	41.3	18.5	--	93.0	47.1	14.28	71.9	
Average values after inhalation of O <sub>2</sub>	--	40.4	19.3	--	97.4	46.4	15.07	75.9	
Average change		0.9*	0.8*		4.4	0.7*	0.79*	4.0	
Percentage of change		-0.46%	+2.3%			-0.67%	+1.8%		

\*Volumes per cent.

and venous blood in the left auricle but depends to some extent on incomplete oxygen saturation of the blood passing through the aerated lung.

The third series of experiments yielded the results shown in Table III. Six animals had uneventful recoveries from the bilateral thoracotomy, one died on the operating table, and one died from postoperative sepsis. In two of the experiments the results were discarded because in one instance the heart action was failing while the blood samples were being withdrawn and in the other, due to deficient aeration, it was necessary to alter the rate of the respirator during the withdrawal of samples.

TABLE III

HEMOGLOBIN, CARBON-DIOXIDE, AND OXYGEN CONTENT, OXYGEN CAPACITY AND OXYGEN SATURATION OF BLOOD SAMPLES FROM (1) PULMONARY ARTERY, (2) RIGHT PULMONARY VEIN, (3) LEFT PULMONARY VEIN, AND (4) LEFT VENTRICLE IN RELATION TO DURATION OF ATELECTASIS, AND PROPORTION OF CARDIAC OUTPUT PASSING THROUGH ATELECTATIC LUNG

DURATION OF ATELECTASIS	DOG 1 142 DAYS	DOG 2 203 DAYS	DOG 3 159 DAYS	DOG 5 191 DAYS	DOG 7 106 DAYS	DOG 8 62 DAYS	AVER- AGE
Pulmonary artery (1)							
Hemoglobin	16.06	15.9	15.4	14.7	13.55	14.4	
Carbon dioxide	41.6	45.2	42.3		49.2		
Oxygen	16.7	14.82	15.44	14.00	10.8	10.8	
Oxygen capacity	21.52	21.3	20.6	19.7	18.2	18.90	
Oxygen saturation	79.3%	69.5%	75.0%	71.0%	59.4%	67.2%	70.2%
Pulmonary vein from right (aerated) lung (2)							
Hemoglobin	16.06	15.75	15.4	14.75	13.55	14.15	
Carbon dioxide	28.1	42.0	35.2		44.0		
Oxygen	21.5	18.6	20.0	19.15	16.35	17.05	
Oxygen capacity	21.52	21.15	20.6	19.8	18.2	18.95	
Oxygen saturation	99.5%	88.0%	97.0%	97.0%	90.0%	90.0%	93.6%
Pulmonary vein from left (atelectatic) lung (3)							
Hemoglobin	16.06	15.52	15.6	14.62	13.65	14.19	
Carbon dioxide	41.0	45.2	46.3		50.0		
Oxygen	15.25	14.1	15.45	14.25	10.7	12.5	
Oxygen capacity	21.52	20.8	20.9	19.6	18.3	19.0	
Oxygen saturation	77.0%	68.0%	74.0%	72.0%	59.4%	65.8%	69.3%
Left ventricle (4)							
Hemoglobin	16.4	15.52	15.4	14.75	13.55	14.4	
Carbon dioxide	30.2	42.6	36.0		45.1		
Oxygen	21.3	17.22	19.15	19.1	16.45	16.0	
Oxygen capacity	22.0	20.8	20.6	19.8	18.2	18.90	
Oxygen saturation	97.0%	83.0%	93.0%	96.4%	90.02%	85.0%	90.7%
Proportion of cardiac out- put through atelectatic lung	6.6%	25.0%	17.3%	2.4%	22.1%	20.6%	15.6%

As expected, oxygen content and saturation were highest in the blood from the aerated lung. The saturation in these samples varied from 88 to 99.5 per cent, with an average of 93.6 per cent. The lowest values for oxygen content and saturation were, of course, in the samples from the pulmonary artery and a left pulmonary vein (collapsed lung),



TABLE II

HEMOGLOBIN, CARBON-DIOXIDE AND OXYGEN CONTENT, OXYGEN CAPACITY AND OXYGEN SATURATION OF ARTERIAL BLOOD AND OXYGEN AND CARBON-DIOXIDE CONTENT AND OXYGEN SATURATION OF VENOUS BLOOD BEFORE AND AFTER INHALATION OF PURE OXYGEN FOR PERIOD OF TEN MINUTES

	HEMO- GLOBIN IN GM.	ARTERIAL CO <sub>2</sub> CONTENT	ARTERIAL O <sub>2</sub> CONTENT	ARTERIAL O <sub>2</sub> CAPACITY	ARTERIAL O <sub>2</sub> SATURATION %	VENOUS CO <sub>2</sub> CONTENT	VENOUS O <sub>2</sub> CONTENT	VENOUS O <sub>2</sub> SATURATION %	DURATION OF ATELEC- TASIS
Experiment 194, 4/9/37	14.92	37.8	17.6	20.0	88.0	43.0	12.7	63.5	198 days
Before breathing pure oxygen	15.0	36.5	19.8	20.1	98.5	41.9	14.7	70.0	
After breathing pure oxygen for 10 min.									
Experiment 200, 4/9/37	14.85	38.6	17.65	19.9	89.0	45.0	14.3	71.4	153 days
Before breathing pure oxygen	14.85	36.6	19.05	19.92	95.8	44.0	14.65	73.5	
After breathing pure oxygen for 10 min.									
Experiment 205, 4/21/37	15.15	45.1	19.5	20.3	96.0	49.5	15.0	73.9	183 days
Before breathing pure oxygen	15.15	43.9	19.8	20.3	97.5	49.0	15.25	74.8	
After breathing pure oxygen for 10 min.									
Experiment 209, 4/26/37	14.25	40.0	18.55	19.1	97.0	44.6	14.24	74.5	187 days
Before breathing pure oxygen	14.25	39.6	19.0	19.1	99.4	43.7	14.65	76.6	
After breathing pure oxygen for 10 min.									
Experiment 210, 4/21/37	14.45	41.5	17.9	19.35	93.0	50.0	14.8	73.2	182 days
Before breathing pure oxygen	14.45	41.4	18.6	19.35	96.0	49.0	16.15	83.0	
After breathing pure oxygen for 10 min.									
Experiment 230, 4/26/37	13.6	41.0	17.15	18.2	94.0	47.7	15.2	83.5	97 days
Before breathing pure oxygen	13.6	40.9	17.45	18.2	96.0	47.7	16.15	88.7	
After breathing pure oxygen for 10 min.									
Experiment 236, 5/3/37	16.1	45.2	21.2	21.65	98.0	50.0	13.75	63.5	58 days
Before breathing pure oxygen	16.1	45.2	21.32	21.65	98.5	49.5	13.99	64.6	
After breathing pure oxygen for 10 min.									
Average values before inhalation of O <sub>2</sub>	--	41.3	18.5	--	93.0	47.1	14.28	71.9	
Average values after inhalation of O <sub>2</sub>	--	40.4	19.3	--	97.4	46.4	15.07	75.9	
Average change		0.9*	0.8*		4.4	0.7*	0.79*	4.0	
Percentage of change		-0.46%	+2.3%			-0.67%	+1.8%		

\*Volumes per cent.

believed that the longer period of atelectasis in our series of experiments has been accompanied by progressive alveolar and capillary collapse and consequently greater decreases in the blood flow through the atelectatic lung.

The effect of chronic atelectasis on the circulation time through the lungs is shown in Table IV. An average of 19.5 seconds was the time necessary for an adequate dose of sodium cyanide to be carried through the atelectatic lung from the point of injection (left branch of the pulmonary artery) to the carotid sinus.<sup>18, 19</sup> When the injection was made into the branch of the pulmonary artery leading to the aerated lung, the average time clapsing before the end point was 9 seconds. The time necessary for sodium cyanide to cause the end point when injected

TABLE IV

PULMONARY CIRCULATION TIME IN RELATION TO DURATION OF ATELECTASIS AND TO PULSE AND RESPIRATORY RATES AS DETERMINED BY INJECTION OF SODIUM CYANIDE INTO RIGHT AND LEFT BRANCHES OF PULMONARY ARTERY

ANIMAL NO.	DURATION OF ATELECTASIS IN DAYS	PULSE RATE	RESPIRATORY RATE	DOSE OF 0.5% SOLUTION OF NACN IN C.C.	CIRCULATION TIME THROUGH ATELECTATIC (LEFT) LUNG IN SECONDS	CIRCULATION TIME THROUGH AERATED (RIGHT) LUNG IN SECONDS
2	203	114		0.18	25.0	
3	159	132		0.18	25.0	9
4	185	72	48	0.25	16.5	11
5	191	128	40	0.2	13.5	8
7	106	156	26	0.2	20.0	7
8	62			0.2	17.0	10
Average					19.5	9
Average	Circulation time from pulmonary artery to carotid sinus				5.0	5
Average	Net pulmonary circulation time*				14.5	4

\*The term, "circulation time through the lungs," used here is defined as the time calculated to be necessary for the passage of blood from either branch of the pulmonary artery to the left ventricle.

into the left ventricle in dogs of similar size and under comparable experimental conditions is 5 seconds,<sup>7</sup> and when this is subtracted from the above average figures, the "net pulmonary circulation time"<sup>18</sup> is 14.5 seconds through the atelectatic lung and only 4 seconds through the aerated lung. It has been shown<sup>7</sup> that within an hour after atelectasis has been produced, the net pulmonary circulation time through the atelectatic lung will be increased from an average normal value of 4.2 seconds to an average value of 6.2 seconds. Accompanying this is a decrease in the net pulmonary circulation time through the aerated lung from a normal average value of 4.6 seconds to an average value of 2.8 seconds. These control values are presented to show that the prolongation of atelectasis with progressive capillary and alveolar collapse leads

\*The term "net pulmonary circulation time" used here is defined as the time calculated to be necessary for the passage of blood from a branch of the pulmonary artery to the left ventricle.

and averaged 70.2 and 69.3 per cent respectively. With the exception of the values for Animal 1, these findings are within the range of normal levels found by Stewart.<sup>16</sup> Their close agreement (within 1 per cent) renders improbable any significant communication between the pulmonary and the bronchial arterial systems in the atelectatic lung.

The oxygen content and saturation of blood from the left ventricle were variable, depending on the admixture of oxygenated and un-oxygenated blood. The figures for oxygen saturation ranged from 85 to 97 per cent and averaged 90.7 per cent. Figures for the carbon-dioxide content of blood from the left ventricle were, in general, higher than those for samples from the aerated lung and lower than those for the samples from the atelectatic lung and the pulmonary artery.

From the figures for oxygen saturation of blood from (1) the left ventricle, (2) a pulmonary vein from the collapsed lung, and (3) a pulmonary vein from the aerated lung, the relative amounts of blood flowing through each lung may be calculated by means of the formula used by Weiss:<sup>17</sup>

$AX + VY = M(X + Y)$  when:

$X$  = percentage of total pulmonary blood flow through the aerated lung

$Y$  = percentage of total pulmonary blood flow through the atelectatic lung

$X + Y = 100$  percentage of the pulmonary blood flow

$X = 100 - Y$

$A$  = oxygen saturation of blood from the aerated lung

$V$  = oxygen saturation of blood from the collapsed lung

$M$  = oxygen saturation of blood from the left ventricle

The calculation for Dog 2, for example, is as follows:

$$88X + 68Y = 83(X + Y)$$

$$8800 - 88Y + 68Y = 8300$$

$$-20Y = -500$$

$Y = 25$  which is the percentage of the cardiac output flowing through the atelectatic lung

$X = 75$  which is the percentage of the cardiac output flowing through the aerated lung

The results in Animals 2, 3, 7, and 8 indicate that between 17 and 25 per cent of the cardiac output passed through the atelectatic lung. The average amount of blood flowing through the atelectatic lung in these four animals was 22 per cent and in the six animals in which the experiment was considered satisfactory, values averaged 15.6 per cent.

Adams<sup>1</sup> employed this method for determining blood flow through lungs made atelectatic for periods varying from one day to ten weeks, by chemical stenosis of the bronchus. In a series of seven animals he found that from 28.5 to 40 per cent (average, 32 per cent) of the total pulmonary blood flow passed through the atelectatic lung. His values are somewhat higher than those presented here and it is

were thickened by deposits of moderately dense fibrous tissue and were infiltrated by plasma cells, lymphocytes, and a few polymorphonuclear leucocytes. These changes extended for a short distance into the adjacent parenchyma. In some areas the bronchial mucosa was unchanged but in others it was represented by a very thin layer of cells. The parenchyma of the lung away from the bronchial tree was singularly free from scarring, fibrosis, and inflammatory reaction. The alveoli were uniformly collapsed. In some areas red blood cells were seen lying in the alveolar spaces. Many of them were partially hemolyzed and hemosiderin had been deposited in phagocytes which were either macrophages or were possibly derived from the alveolar walls. The presence of these cells in the alveoli made the lung more solid than could be accounted for by the atelectasis alone. No evidence of communications between the blood and the air channels was found in the study of these sections. The quantity of blood in the alveolar spaces was small compared to the potential capacity of the spaces and apparently was the result of diapedesis.

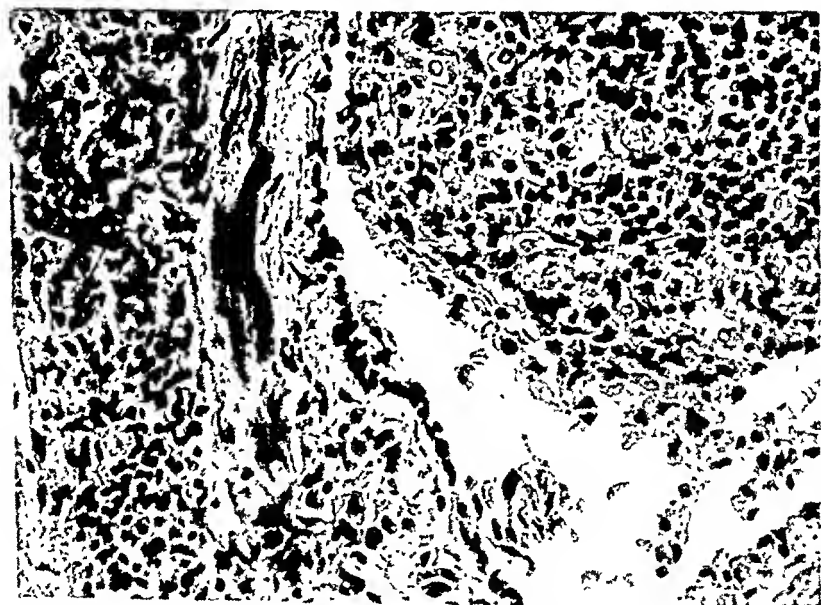


Fig. 4—The bronchial wall is thick and is infiltrated with lymphocytes and macrophages. There is beginning fibrous tissue replacement of the muscular coat. The lumen contains an inflammatory exudate.

Adams<sup>1</sup> found dilated spaces filled with apparently normal blood in the lung parenchyma within two months after the production of atelectasis by chemical stenosis of the bronchus. At the end of six months these spaces were present in large areas of the lung and also surrounding the larger bronchi. Of the animals studied here, four had atelectasis for six months or longer, two had atelectasis for more than

to marked decrease in the rate of blood flow through the collapsed lung. However, the increase in the speed of blood flow through the aerated lung, seen soon after the production of atelectasis, does not persist but is followed by a return to normal values within six months.



Fig. 3.—Section of dilated bronchus filled with mucoid material and macrophages. The wall of the bronchus is edematous and is infiltrated by plasma cells, lymphocytes, and a few polymorphonuclear leucocytes. Leucocytic infiltration and scarring extend for a short distance into the parenchyma.

The significant findings at autopsy were confined to the chest. The heart and left lung were found to occupy the left half of the thorax. The atelectatic lung was bluish purple and, in most of the animals, it was adherent to the chest wall along the thoracotomy wound. In three of the animals additional areas of adhesions were found over the costal surfaces but none was extensive. Some adhesions were also present on the mediastinal surface near the hilus. The main vessels at the hilus appeared to be decreased in size when compared to those of the opposite side. The divided ends of the bronchus were adherent to each other in some of the animals but in none was there a communication between them. The obstructed left main bronchus and its branches were filled with mucoid material. No areas of suppuration were seen on gross examination.

The principal points of interest in the microscopic examination were found in the collapsed lung (Figs. 3, 4, and 5) to which the following description, in general, applies. The bronchial radicals were dilated and contained bluish pink staining mucoid material in which varying numbers of macrophages were seen. The walls of the bronchial branches

Early in the course of the atelectasis the circulation time from a leg vein to the carotid sinus as determined by the injection of sodium cyanide is decreased but tends to return to basal values during the second month of atelectasis. At this time the blood gases also return to basal levels. During the fourth month of atelectasis there is a second decrease in the leg to carotid sinus circulation time but it is unaccompanied by any alteration in the blood gases. A second return to basal levels of circulation time is found during the fifth or sixth month. Since the greater part of the cardiac output passes through the aerated lung, most of the sodium cyanide passes through it also. The values for circulation time determined in this way consequently indicate the rate of blood flow through a vascular circuit of which the aerated lung forms a part. The changes in the circulation time are therefore thought to be due to alterations in the rate of blood flow through the aerated lung rather than to increased rates of flow in the peripheral vascular system. It has been shown in acute experiments that the rate of blood flow through a lung recently rendered atelectatic is decreased. By direct studies of the circulation time through the atelectatic lung it has been demonstrated that the continued state of atelectasis is accompanied, after several months, by further decreases in the amount and velocity of blood flowing through the affected lung, these decreases being brought about most probably by progressive alveolar and capillary collapse.

The degree of oxygen unsaturation in the peripheral arterial blood accompanying atelectasis of from 58 to 198 days' duration has been shown to be due to two factors: (1) the unsaturation of blood passing through the aerated lung and (2) the admixture of oxygenated blood from the aerated lung and unoxygenated blood from the collapsed lung. In the same animals, after these periods of atelectasis, by studying the oxygen saturation of blood from the functioning lung, from the collapsed lung and from the left ventricle, the amount of blood passing through the atelectatic lung during intermittent insufflation of the opposite lung with the chest open was found to average 15.6 per cent of the cardiac output.

#### CONCLUSIONS

Atelectasis of one lung of from 58 to 198 days' duration produced experimentally in dogs results in the following:

1. A variable decrease in the oxygen saturation and a less constant increase in carbon-dioxide content of arterial and venous blood in resting animals. These changes persist for a period of from four to six weeks.
2. No significant changes in the hemoglobin, hematocrit, or in the total plasma volume.
3. A decrease in the leg to carotid sinus circulation time during the first month of atelectasis, a return to basal levels during the second

five months, and the other two for approximately two months. The sections from these animals represented portions of lung both from the periphery and from areas surrounding the larger bronchi, yet no blood spaces such as those described by Adams were found.

#### SUMMARY

The principal changes which follow the production of experimental atelectasis in dogs by the division and closure of a bronchus may be summarized as follows: Within a few minutes after the bronchus is divided the blood circulating through the corresponding lung begins to absorb the contained gases and there appear areas of discoloration indicating atelectasis. This process continues until practically no gases remain in the lung, which then resembles a solid organ such as the liver. During this time there is a shift of blood flow from the

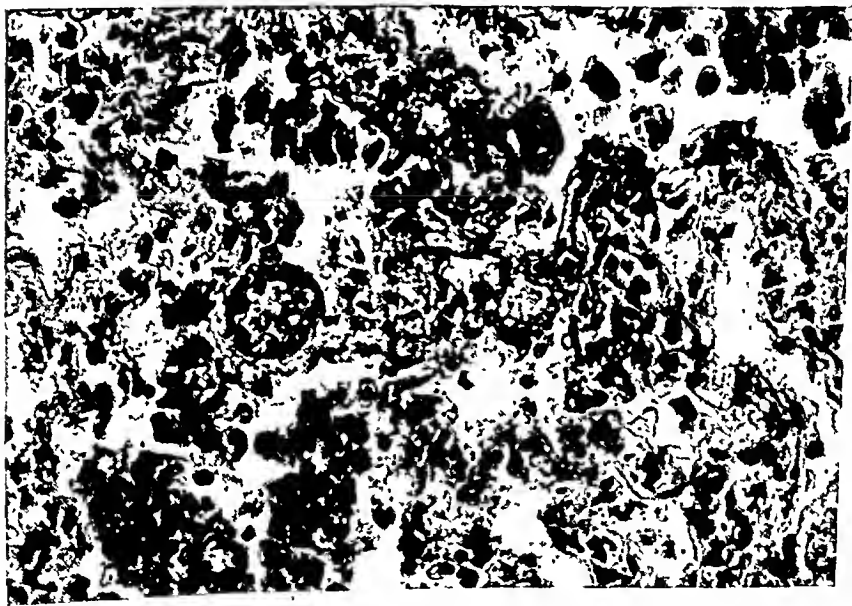


Fig. 5.—Lung parenchyma showing uniformly collapsed alveoli. Macrophages containing ingested material are present in the shrunken alveolar spaces.

atelectatic to the aerated lung. Thereafter for a period of weeks sufficient blood flows through the collapsed lung to cause a variable degree of oxygen unsaturation of peripheral arterial blood due to the admixture of oxygenated and unoxygenated blood in the left auricle. However, this degree of arterial anoxemia is not sufficient to cause any significant increase in hemoglobin, hematocrit, or total plasma volume. The proportion of the cardiac output which passes through the atelectatic lung decreases, causing an increase in the oxygen saturation of peripheral blood, and after a period of from six to eight weeks there is a negligible degree of oxygen unsaturation in the resting animal.

14. Livingstone, H., and Adams, W. E.: Bacterial Flora of the Lower Respiratory Tract in Dogs, *J. Infect. Dis.* 48: 282-291, 1931.
15. Gibson, J. G., Keeley, J. L., and Pijoan, Michael: The Blood Volume of Normal Dogs, *Am. J. Physiol.* 121: S00-S06, 1938.
16. Stewart, H. J.: Oxygen and Carbon Dioxide Contents of Arterial and Mixed Venous Blood in Normal Intact Dogs, *J. Biol. Chem.* 62: 641-647, 1925.
17. Weiss, R.: Ueber die Durchblutung der Kollapslung beim experimentellen pneumothorax, *Ztschr. f. d. ges. exper. Med.* 53: 138, 1926.
18. Heymans, C., Bouekaert, J. J., and Dautrebande, L.: Sinus carotidien et reflexes respiratoires; sensibilité des sinus carotidiens aux substances chimiques; action stimulante respiratoire reflexe du sulfure de sodium, des cyanure de potassium de la nicotine et de la lobeline, *Arch. internat. de pharmacodyn. et de therap.* 40: 54-91, 1931.
19. Owens, H., and Gessell, R.: Peripheral and Central Chemical Control of Pulmonary Ventilation, *Proc. Soc. Exper. Biol. & Med.* 28: 765-766, 1931.



month, a secondary decrease during the fourth month, and a secondary return to basal levels during the fifth or sixth month.

4. Oxygen unsaturation of peripheral blood which is due to two factors: (1) oxygen unsaturation of blood passing through the aerated lung and (2) admixture of oxygenated blood from the aerated lung and unoxygenated blood from the collapsed lung.

5. A decrease in the proportion of the cardiac output which passes through the atelectatic lung. After 58 to 198 days of atelectasis only an average of 15.6 per cent of the cardiac output passes through the atelectatic lung when the chest is open and the other lung is insufflated intermittently.

6. A decrease in the size of the corresponding pulmonary vessels, uniformly collapsed alveoli containing partially hemolyzed red blood cells and phagocytes containing hemosiderin, an accumulation of mucoid material in the bronchial radicals and thickening and chronic inflammatory changes in their walls and no scarring, fibrosis or inflammatory changes in the lung parenchyma except immediately adjacent to the bronchial tree.

We wish to express our appreciation to Dr. Edward L. Burns for his assistance in the interpretation of the microscopic findings and in the preparation of the photomicrographs.

#### REFERENCES

1. Adams, W. E., Hrdina, L., and Dostal, L. E.: Vascular Changes in Experimental Atelectasis; Morphological, Physiological, and Biochemical, *J. Thoracic Surg.* 4: 377-398, 1935.
2. Andrus, W. DeW.: Observations on the Cardiorespiratory Physiology Following the Collapse of One Lung by Bronchial Ligation, *Arch. Surg.* 10: 506-519, 1935.
3. Bruns, O.: Ueber die Blutzirkulation in der atelektatischen lunge, *Deutsches Arch. f. klin. Med.* 108: 469-493, 1912.
4. Coryllos and Birnbaum: The Circulation in the Compressed, Atelectatic and Pneumonic Lung, *Arch. Surg.* 19: 1346, 1929.
5. Dock and Harrison: The Flow of Blood Through the Lungs in Experimental Pneumothorax, *Am. Rev. Tuberc.* 10: 534, 1925.
6. Fine, J., and Drinker, C. K.: The Effect of Atelectasis on the Pulmonary Blood, *Arch. Surg.* 22: 495-502, 1931.
7. Keeley, J. L.: Circulation Time Through Aerated and Atelectatic Lungs in Dogs as Determined by the Use of Sodium Cyanide, *Am. J. Physiol.* 132: 93-98, 1941.
8. Moore, R. L.: The Volume of Blood Flow Per Minute Through the Lungs Following Collapse of One Lung by Occlusion of Its Bronchus, *Arch. Surg.* 22: 225-257, 1931.
9. White and Gammon: Some New Features of Interest About the Pulmonary Circulation and the Fate Therein of Intravenously Introduced Fats, *Tr. Nat. Tuberc. A., Tenth Annual Meeting*, pp. 215-220, 1914.
10. Van Slyke and Neill: Determination of Gases in Blood and Other Solutions by the Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.* 61: 523-573, 1924.
11. Evelyn, K. A.: Stabilized Photoelectric Colorimeter With Light Filters, *J. Biol. Chem.* 115: 63-75, 1936.
12. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume, I. Clinical Application of a Method Employing the Azo-Dye "Evans Blue" and the Spectrophotometer, *J. Clin. Investigation* 16: 301-316, 1937.
13. Loevenhart, A. S., Schlomovitz, B. H., and Seybold, E. G.: Determination of Circulation Time in Rabbits and Dogs and Its Relation to Reaction Time of Respiration to Sodium Cyanide, *J. Pharmacol. & Exper. Therap.* 19: 221-238, 1922.

the light of observations upon experimental hypertension due to renal ischemia. It is now generally accepted that in this type of experimental hypertension, there may be no demonstrable variation from the normal anatomic structure or function of the kidneys. Controls have demonstrated that hypertension will result from partial ischemia of the kidney irrespective of its innervation. The presence of the adrenal medulla is not necessary, but the adrenal cortex is essential. The large body of evidence indicating that the partially ischemic kidney exerts its effects through a humoral mechanism has been reviewed by Page (1940). Analysis of the available data by Munoz and co-workers (1940) and independently by Page (1940) and others has yielded schemata indicating the mode of formation of the substances producing hypertension after renal ischemia. The schemata show a remarkable similarity in spite of differences in nomenclature. Finally, Page and Helmer (1940) reported the isolation and crystallization of the pressor substance as the oxalate and picrate.

The principal goal in clinical investigation is the application of relevant data to the eradication of disorders in man or to the relief of their effects. In the case of human hypertension there are gaps in the knowledge not only concerning the role played by the kidneys but also concerning the details of the production and the nature of the humoral substances involved. Nevertheless, encouraging steps have already been taken in the direction of controlling at least the symptoms and signs of hypertension in man (*cf.* Grollmann, Williams and Harrison, 1940; Page and associates, 1941). These attempts at therapy with extracts of normal kidneys were stimulated by the knowledge that the normal kidney inhibits or counteracts the actions of the substances liberated by the ischemic kidney. Page and his co-workers (1941) have reported suggestive preliminary results from the oral administration of renal extracts in cases of malignant hypertension.

Further progress in the etiology and therapy of hypertension awaits an increased understanding of the nature of the products of the ischemic kidney, their biologic effects, and the mechanism by which the normal kidney or its extracts counteract the effects of the ischemic kidney.

Most of the observations in the past have been made on the effects of long-standing partial ischemia of the kidneys, or on test animals into which extracts of normal or ischemic kidneys have been injected. It was thought desirable to study the immediate effects of short-lasting but total ischemia of the kidney not in a second test animal, but in the same animal. In addition to obtaining data concerning the systemic effects of substances produced by or in the ischemic kidney, it was planned to become sufficiently familiar with the technique to evaluate its usefulness for testing the effects of crude extracts or of purified substances upon the results of injecting the products of the ischemic kidney. This paper concerns the results of these experiences.

## SOME OBSERVATIONS ON ACUTE RENAL HYPERTENSION

WM. C. QUINBY, M.D., AND F. A. SIMEONE, M.D., BOSTON, MASS.

*(From the Urologic Clinic of the Peter Bent Brigham Hospital and the Laboratories of Physiology and Surgical Research in the Harvard Medical School)*

IN 1836, Bright first suggested that hypertrophy of the heart found in patients dead of kidney disease might be secondary to the increased pressure or resistance offered by the kidneys against which the heart was forced to drive in order to maintain the circulation. Blood pressure was not mentioned, but the implication was obvious, and since that time numerous investigations have been made of the relationship between disorders of the kidney and arterial hypertension.

The earliest studies concerned statistical analyses of the relationship between disease in the kidney and clinical hypertension. They were enhanced by the introduction of a convenient method for determining the blood pressure in man by Riva-Rocci in 1895. The data were confusing, however, and it was practically impossible to distinguish between cause and effect. Further advance in the problem had to await the development of applicable laboratory techniques.

Tigerstedt and Bergmann (1898) demonstrated that saline extracts of the kidney induced a rise in the blood pressure when injected intravenously into the experimental animal. Though others at first were unable to obtain such positive data, satisfactory confirmation was reported by Bingel and Strauss (1909) and by Bingel and Claus (1910). These observations were confirmed and further extended by Landis, Montgomery, and Sparkman (1938). At best, however, this evidence that the kidneys contain substances capable of elevating the blood pressure in experimental animals is quite indirect as far as the relationship between the kidney and clinical hypertension is concerned.

Recently important advances have been made by the use of methods devised to induce hypertension by interfering with the circulation of the kidney (see Goldblatt, 1938, for references). The method of inducing partial ischemia of the kidneys (Goldblatt and associates, 1933) and that of producing a constrictive perinephritis by means of cellophane (Page, 1939) have been the most consistent in producing hypertension experimentally and have yielded, to date, the most valuable information concerning the role the kidneys play in experimental and clinical hypertension.

The fact that hypertension in man may exist in the absence of any anatomical or functional evidence of disease of the kidneys has been offered repeatedly as evidence that the kidneys play no significant part in clinical hypertension. This criticism has lost its weight, however, in

denervation of the heart. In the other the right adrenal gland was excised at the time of the first stage of cardiac denervation and the other was removed acutely at the time of the experiment six weeks later. In both these animals central stimulation of the sciatic nerve increased the heart rate by only four to six beats per minute when this test was made before the acute experiment was begun.

In 2 of the cats the spinal cord was transected at the level of C7 to provide a low initial blood pressure and to avoid reflex effects. This procedure proved unsatisfactory and will be discussed below (*cf.* effects of low initial pressure).

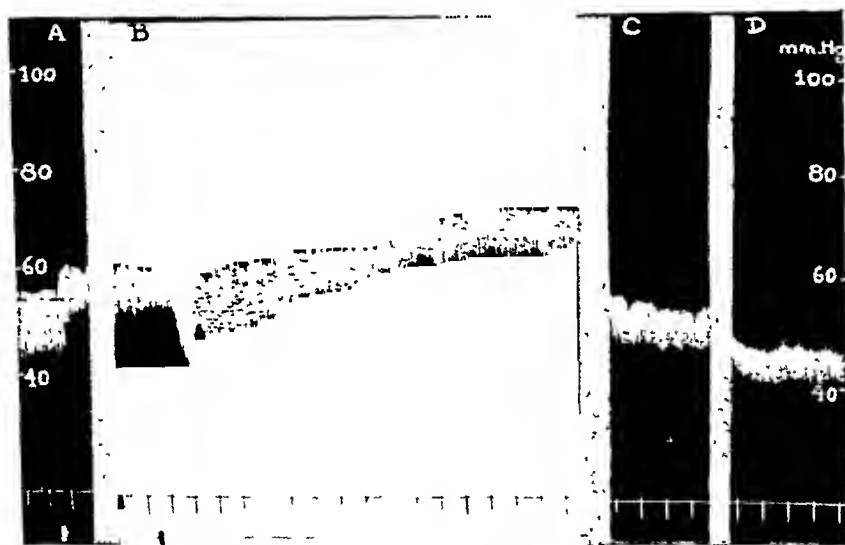


Fig. 2.—Dog 1 (Aug. 8, 1940). Urethane anesthesia (1.75 Gm. per kilogram). Tracing of blood pressure with Hürthle manometer calibrated against mercury manometer. Scales at right and left represent blood pressure in millimeters of mercury. Both vagi cut in neck. Adrenal glands removed acutely. Aorta ligated below origin of renal arteries. At first signal, clamp was applied to aorta above level of origin of renal arteries; at second signal, clamp was released. Note passive rise and fall of the blood pressure with application and release of clamp. The heart rate at the maximum rise was 206 per minute, during the fall, 210 per minute. Interval between A and B, 4 minutes; between B and C, 22½ minutes; between C and D, 8½ minutes. Time signal, 30 seconds.

The blood pressure records were made on a smoked-drum kymograph by means of a rubber-membrane Hürthle manometer and in the 2 dogs in which the heart was denervated and the adrenals removed, by means of the direct mercury manometer.

## RESULTS

1. *Repeatability of the Pressor Response.*—A rise in blood pressure was obtained in 5 of the 10 cats after release of the occluded renal arteries. The cause for the failures will be discussed below. A rise in blood pressure upon release of the occluded renal pedicle was obtained in every one of the 7 dogs tested.

## MATERIAL AND METHOD

The experiments were performed upon 10 adult cats and upon 7 adult dogs weighing 7 to 12 kg. All experiments were done under urethane anesthesia (1.5 to 1.75 Gm. per kilogram intravenously) induced slowly and usually with the animal under a preliminary ether anesthesia. Records of the blood pressure were made from the earotid artery, usually the right. The contralateral earotid artery was ligated to exclude the earotid sinus from the eirculation. Both vagi and both cervial sympathetic trunks were severed in the neck. In 2 dogs in which the heart had been denervated at a previous operation, the inferior cervial ganglia were excised along with the vagi through the base of the neck at the time of the experiment.

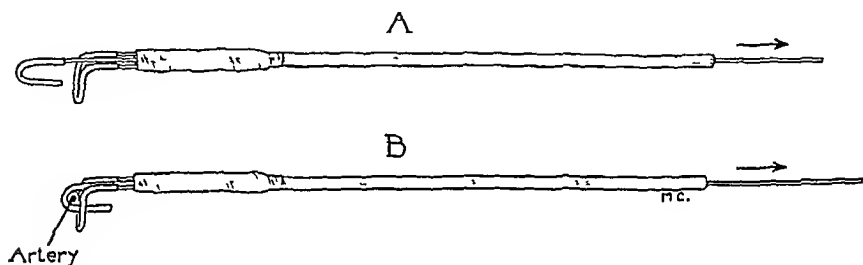


Fig. 1.—Clamp used for occluding the aorta or renal arteries (constructed by Miss E. M. Bright). The clamp was set by a screw-clamp holding the style against its sheath after having drawn it up to occlude the vessel

Sudden complete ischemia of the kidneys was produced by means of delicate rubber-covered adjustable elamps (Fig. 1). In every case the kidneys were exposed through either a single upper abdominal midline incision or each kidney separately through a subcostal flank incision. Both kidneys were always thoroughly freed from the perinephrium to interrupt any accessory blood supply reaching the kidney through its cortex from the perinephrium. The dissection included clearing the renal pedicle so as to denervate the kidney. In 3 cats and 1 dog the clamp was applied on the aorta above the origin of the renal arteries after ligating it below the origin of the arteries. In all of them the adrenal glands were removed acutely to eliminate the effects of ischemic adrenal glands. In the rest of the animals the elamps were applied one to each renal pedicle including all the arterial branches to the kidney and excluding the veins.

In 2 dogs it was desired to test the humoral effects upon the heart of releasing the totally ischemic kidney. For this purpose sympathetic denervation of the heart was carried out as described by Cannon and his co-workers (1926). The vagi and the inferior cervical ganglia were resected acutely at the time of the experiment one and two months after the sympathetic denervation. In 1 of these animals the right adrenal gland was removed and the left demedullated at the first stage of

denervation of the heart. In the other the right adrenal gland was excised at the time of the first stage of cardiac denervation and the other was removed acutely at the time of the experiment six weeks later. In both these animals central stimulation of the sciatic nerve increased the heart rate by only four to six beats per minute when this test was made before the acute experiment was begun.

In 2 of the cats the spinal cord was transected at the level of C7 to provide a low initial blood pressure and to avoid reflex effects. This procedure proved unsatisfactory and will be discussed below (cf. effects of low initial pressure).

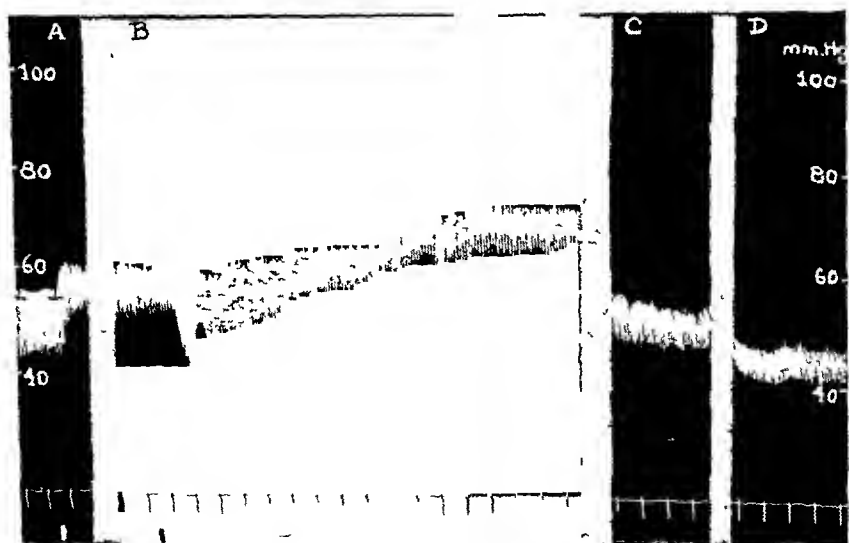


Fig. 2.—Dog 1 (Aug. 8, 1940) Urethane anesthesia (1.75 Gm per kilogram). Tracing of blood pressure with Hürthle manometer calibrated against mercury manometer. Scales at right and left represent blood pressure in millimeters of mercury. Both vagi cut in neck. Adrenal glands removed acutely. Aorta ligated below origin of renal arteries. At first signal, clamp was applied to aorta above level of origin of renal arteries. At second signal, clamp was released. Note passive rise and fall of the blood pressure with application and release of clamp. The heart rate at the maximum rise was 206 per minute, during the fall, 210 per minute. Interval between A and B, 4 minutes; between B and C, 22½ minutes; between C and D, 8½ minutes. Time signal, 30 seconds.

The blood pressure records were made on a smoked-drum kymograph by means of a rubber-membrane Hürthle manometer and in the 2 dogs in which the heart was denervated and the adrenals removed, by means of the direct mercury manometer.

## RESULTS

1 *Repeatability of the Pressor Response.*—A rise in blood pressure was obtained in 5 of the 10 cats after release of the occluded renal arteries. The cause for the failures will be discussed below. A rise in blood pressure upon release of the occluded renal pedicle was obtained in every one of the 7 dogs tested.

2. *Relationship Between Duration of Ischemia and Magnitude of Pressor Response.*—The shortest period of occlusion tested was three minutes. This produced a definite rise in blood pressure after release of the clamps in the dog but not in the cat. The rise in blood pressure was only about 10 mm. of mercury, however, and its duration was not longer than ten to fifteen minutes. Ischemia of five minutes' duration led to hypertension in both cat and dog. Occlusion for periods of ten minutes produced blood pressure rises which were similar in degree and duration to the pressor responses after periods of occlusion lasting longer than ten minutes (Figs. 2 and 3). The longest occlusion was for five and one-half hours.



Fig. 3.—Dog 2 (Aug. 16, 1940). Preparation as in Fig. 2 except that clamps were applied to renal arteries instead of aorta. First signal: both renal pedicles clamped (excluding veins), for 74 minutes. Second signal: clamps released. Note composite character of pressor response (see text). Interval between A and B, 67 minutes. Time signal, 30 seconds.

The average blood pressure rise obtained in the cat was 30 mm. of mercury. The maximum rise was 40 mm. of mercury after both renal pedicles were clamped for five hours. A rise of 33 mm. of mercury was obtained after the pedicles were clamped for only ten minutes. The average blood pressure rise obtained in the dog was 40 mm. of mercury. The maximum rise was 80 mm. of mercury after the arteries to the kidneys were clamped for 105 minutes (Fig. 4). In general, beyond the period of ten minutes the duration of the renal ischemia had no consistent influence upon the degree of rise in blood pressure after release of the occlusion.

3. *The Time Course of the Changes in Blood Pressure After Release of Renal Ischemia.*—Immediately upon releasing the occluding pedicle clamps, there was a passive drop in the blood pressure level, the counterpart of the passive rise in blood pressure observed when the clamps

were applied. When the period of ischemia was prolonged, the blood pressure often fell slowly from the initial passive rise while the clamps were still in place and sometimes no immediate fall was seen on releasing the clamps (Fig. 4). Usually, though not always, there was a brief drop in blood pressure below the level accounted for by passive opening of the renal vascular bed. The duration of this drop was never more than about forty-five seconds before a definite rise in the blood pressure tracing could be recognized. Within three minutes the basal blood pressure level was reached, but the maximum rise was not reached for from six to twelve minutes in different experiments. In the same experiment the peak of the rise in blood pressure was delayed by repetition of the occlusion. In 1 dog, for instance, the peak was reached eight minutes after release of the occluding clamps the first time, while it was delayed to thirty-two minutes after the third occlusion. This latent period was

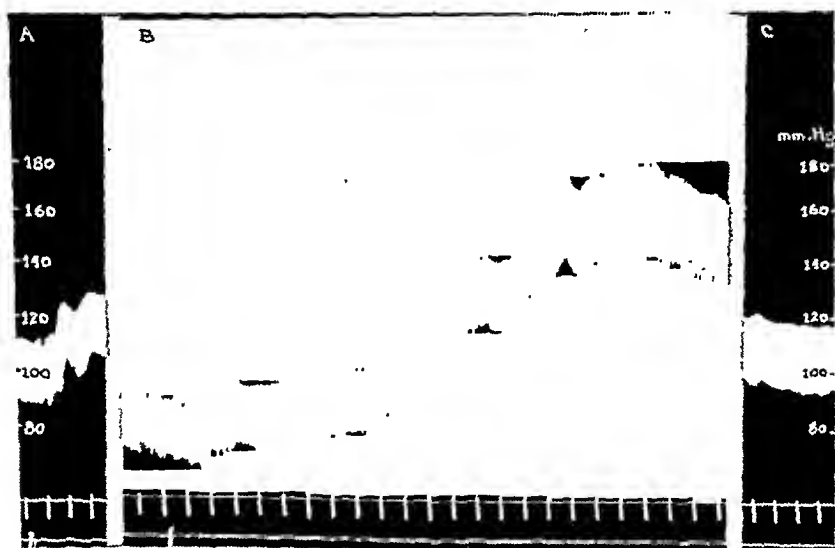


FIG. 4.—Dog 3 (Sept. 20, 1940). Preparation as in Fig. 3. Clamps applied to renal arteries at first signal and released at second signal 105 minutes later. Interval between A and B, 103 minutes, between B and C, 22½ minutes. The blood pressure fell slowly while the clamps remained applied. Note that there is no passive fall in blood pressure after release of the clamps.

not related to the duration of occlusion, and it was generally longer in the cat than in the dog. The increased delay in reaching the peak of the pressor response after successive occlusions may be due to injury to which the more delicate renal arteries of the cat are more susceptible than those of the dog.

The average duration of the rise in blood pressure of the cat following release of the occluding clamps was twenty-nine minutes. The maximum and the minimum durations were forty-five and fifteen minutes respectively. In the dog the average duration of hypertension was thirty-three minutes; the maximum was forty minutes and the minimum was



twenty minutes. As observed for the time required to reach the maximum pressor effect, the duration of the hypertension was independent of the duration of the occlusion beyond the ten-minute period. Dicker (1937), in fact, reported pressor effects in the dog lasting only twenty to thirty minutes after releasing renal arteries which had been ligated for twenty-four hours.

4. *Effect of Initial Blood Pressure Upon Development of Hypertension After Release of Renal Ischemia.*—Three of the 5 cats in which no rise of blood pressure was obtained after release of the occluding clamps had initial blood pressures of 60 to 45 mm. of mercury. One of these 3 cats had its spinal cord transected at C7 and both adrenals removed acutely; another had only both adrenals removed; the third had spinal transection at C7 while the adrenals remained intact. Common to all 3 animals was the low initial blood pressure. In none of them was there the passive rise and fall of blood pressure with application and release of the clamps.

Three of the 7 dogs used in these experiments had initial blood pressures under 100 mm. of mercury (92, 72, and 50 respectively). They all gave typical blood pressure responses after releasing the occluding clamps. The dog with the lowest initial blood pressure had had its adrenal glands removed acutely. Nevertheless, when the occluding clamps were released after having been applied for only five and one-half minutes, there was a rise of 25 mm. in blood pressure returning to normal after forty minutes. It appears that, at least in cats, a head of pressure (60 mm. of mercury) is necessary to re-establish the circulation through the previously occluded renal vessels.

5. *Tachyphylaxis.*—Repeated injections of renin have been shown to be progressively less effective in producing the typical rises in blood pressure. This phenomenon was observed first by Tigerstedt and Bergmann (1898) and to it has been applied the term "tachyphylaxis." Repeated occlusions and releases of the renal arteries have shown no evidence of tachyphylaxis in either cat or dog. In no experiment, however, was the occlusion and release repeated more than four times and this may not have been a sufficient number of times to demonstrate the phenomenon.

6. *Effects Upon the Heart.*—In two experiments, an apparent increase in the pulse pressure was observed. In two others, at the height of the blood pressure response, there was a rise in pulse rate to fourteen and eighteen beats per minute above basal respectively. Since these observations were made (a) with the Hürthle manometer which might introduce an artefact in the apparent pulse pressure, and (b) in animals with the sympathetic nerve supply to the heart intact so that the basal rate was usually above 200 per minute and reflex changes were possible, two experiments were done in dogs with direct recording from a mercury manometer, with the heart denervated and with the possibility of adrenal

medullary effects removed. The respiratory rate and amplitude were recorded in these animals by means of a tambour connected with the tracheal cannula through a shunt. There was no evidence of change in pulse pressure, heart rate, or respiratory rate after release of the occluded vascular supply to the kidney. The usual respiratory irregularities due to urethane anesthesia were observed in 1 of the dogs, but these were shown to have no effect on the blood pressure, pulse pressure, or heart rate.

#### DISCUSSION

In 1905 Katzenstein applied ligatures to the renal pedicles of a curarized dog and released them after thirty-seven minutes of partial occlusion and 177 minutes of complete occlusion. He observed a rise in the arterial blood pressure beginning about three minutes after release of the occlusion, reaching a plateau after eighteen minutes and returning to the initial blood pressure after a half-hour. He attributed this observation to the effects of suspected thrombosis in the renal arterioles rather than to any humoral effect. Indeed, the humoral effects of acute renal ischemia were not recognized until more than three decades later. After the work of Goldblatt and his associates (1933) had demonstrated that chronic partial renal ischemia can cause arterial hypertension through a humoral agency, experiments were reported showing that acute renal ischemia was able to effect a rise in the arterial blood pressure by a similar mechanism (*cf.* Taquini, 1938, 1940). More recently, these observations have been extended by Collins and Hamilton (1940); Prinzmetal, Lewis, and Leo (1940); and Leo, Prinzmetal, and Lewis (1940).

A theory, or "working hypothesis," has been formulated concerning the nature of the humoral mechanism concerned in renal hypertension, (Munoz and associates, 1940; Page, 1940). The ischemic kidney is thought to liberate a substance, *renin*, which, as an enzyme, acts upon a substrate, *hypertensinogen*; or *hypertensin precursor*, present in the pseudoglobulin fraction of blood serum. A new substance, *hypertensin*, is thereby formed which causes arterial hypertension by effecting a diffuse arteriolar constriction. Prolonged incubation of renin and hypertensinogen results in a low yield of hypertensin, presumably due to destruction of this substance by a second enzyme, *hypertensinase*, present in the blood. Hypertensinase is produced by or in the kidney and is destroyed in strongly acid solutions. Hypertensin is called *angiotonin* by Page who has interpreted renin not as an enzyme but as a precursor of angiotonin. A number of properties of renin, however (*cf.* Munoz and co-workers, 1940), favor its enzymatic character.

The experiments reported in this paper indicate a liberation of a multiplicity of substances from the kidney. Some of the experiments showed a preliminary drop in blood pressure below the basal level before

the pressor response became manifest. In 2 cats, in fact, the blood pressure fell precipitously and the animals died (Fig. 5). Other tracings exhibited quick rises in arterial blood pressure superimposed early upon the slow rise characteristic of the renin response (Fig. 3). The rapid adrenaline-like pressor effects may be due to the liberation of hypertensin (or angiotonin) in small amounts. This observation is in agreement with that of Williams and Grossman (1938) who obtained two pressor substances from the ischemic kidney, a heat-stable adrenaline-like substance, and a heat-labile reninlike substance. The rarity with which hypertensin effects were produced in the above experiments supports the evidence recently reported by Prinzmetal, Lewis, and Leo (1940) that the pressor substance liberated after release of complete renal ischemia is renin.

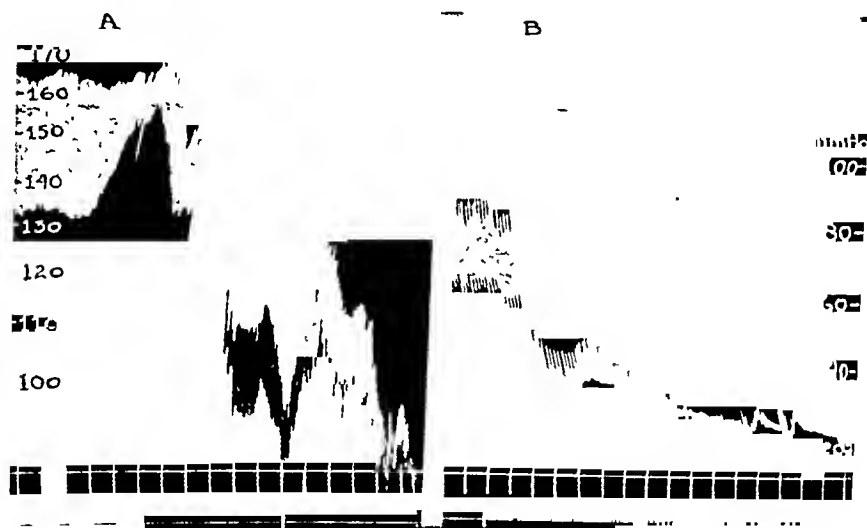


Fig. 5.—A. Cat 3. B. Cat 6. Urethane (1.5 Gm. per kilogram). Tracings of blood pressure from right carotid artery. Left carotid ligated. Both vagi cut in neck. Calibration of Hürthle manometer as in other figures. Clamps on renal arteries in A; on aorta above origin of renal arteries in B. Adrenal glands intact in A; excluded from circulation in B. In A (June 22, 1940), clamp removed from right renal vessels at first signal and from left renal vessels at second signal. Note temporary pressor effect upon releasing the second clamp. In B (July 11, 1940), the clamp was removed from the aorta at the signal, five hours after application. Heart rate, 226 per minute.

Schroeder and Steele (1940) have reported evidence that the kidneys possess a mechanism whereby they can maintain their blood flow within limits in spite of changes elsewhere in the systemic circulation. If the passive rise and fall of arterial pressure after occlusion and release respectively of the renal arteries is taken as a sign of active blood flow through the kidney (Figs. 2 and 3; Alwens, 1909), the results recorded above indicate that when the systemic arterial blood pressure has fallen below 60 mm. of mercury the blood flow through the kidney is either diminished or abolished. While causing at least a temporary fall in general arterial blood pressure, there is no evidence that sympathectomy or splanchnectomy induces an increase in the blood flow through the kidney

(Smith and associates, 1939). Consequently, the rationale of sympathectomy in arterial hypertension can logically be questioned. As far as the brain, heart, and kidneys are concerned, a reduction in the blood pressure by shunting blood elsewhere than through these organs is the equivalent of bloodletting. To be of therapeutic value, the drop in blood pressure should be effected by some agent which will cause a *generalized* reduction of the peripheral resistance.

The blood pressure tracings obtained following release of complete renal ischemia resemble very closely those obtained by injection of purified or crude renin. The usual absence of immediate hypertensin effects in the records may be due to destruction of this substance by hypertensinase in the kidney. Of especial interest are the facts that only a very short period of total ischemia is necessary for the production of hypertension and that beyond the minimum period of three to ten minutes longer durations do not appreciably affect the degree or duration of the rise in arterial hypertension. This may be explained on the assumption that the substance elaborated by renal ischemia is primarily renin, the reaction of which with hypertensinogen is not stoichiometric so that quantitatively the limiting reactor is hypertensinogen present preformed in the blood. Within limits, therefore, small amounts of renin liberated during short periods of ischemia would be as effective as larger amounts produced during longer periods.

The mechanism whereby renal ischemia causes the liberation of pressor substances into the blood stream is not understood. Kohlstedt and Page (1940) have presented evidence that the important result of occlusion of the renal artery for the liberation of pressor substances into the blood stream is the reduction in pulse pressure. They demonstrated that the liberation of renin from the "ischemic" kidney was independent of the mean arterial pressure in the kidney but could be effected by diminution of the pulse pressure even though the mean arterial pressure was maintained at a normal level. The site of liberation or production of the pressor substances is likewise unknown. They may be produced in the convoluted tubules of the kidney. Goormaghtigh (1940) believes that the substances are produced in the "juxtaglomerular apparatus" of the kidney. This consists of cells between the afferent and efferent branches of the glomerular arterioles adjacent to the proximal convoluted tubule. He has interpreted them as modified smooth muscle cells. It is not unlikely that a number of different mechanisms may be involved. Thus Bing and Zucker (1941) and Bing (1941) have reported the production of a potent pressor substance formed by the anaerobic decarboxylation of "dopa" by human and guinea pig renal cortex.

The experiments reported here suggest that the adrenal cortex plays no role in the immediate liberation of pressor substances by the ischemic kidney. The effects of chronic adrenal cortical deficiency in preventing

the pressor response to chronic renal ischemia may be due to a modification of the arteriolar effectors rather than to an interference with the production of pressor substances.

Although many pharmacologic properties of hypertensin are known (*cf.* Munoz and associates, 1940; Page, 1940), the chemical nature of the pressor substances released by ischemic kidneys remains obscure. Further data are required to determine the possible role of hydroxytyramine (Bing, 1941). The mechanism of the hypertension following release of renal ischemia is an increase in the peripheral resistance by arteriolar constriction. The experiments reported above in dogs with denervated hearts and absent adrenal medullae showed no indication of any effect upon the cardiac output or the heart rate.

The presence of an intact normal kidney inhibits the hypertensive effects of ischemia of the other kidney and hastens the return to normal blood pressure following extirpation of the ischemic kidney. The logical implication has been that the normal kidney through the agency of hypertensinase or some similar mechanism counteracts the effects of the pressor substances liberated from the ischemic kidney. Application of these data has resulted in the administration of extracts of normal kidney by Grollman, Williams, and Harrison (1940[a]) and by Page (1940) to hypertensive rats and dogs, with encouraging results. Grollman, Williams, and Harrison (1940[b]) and Page and his co-workers (1941) have treated patients with essential and malignant hypertension with extracts of normal hog kidneys. Although their observations require confirmation, extension, and further control, the results which they have reported are at least suggestive. The experiences of Schroeder (1941) with tyrosinase and those of Wakerlin and Johnson (1941) with the immunologic aspects of hypertension, though only preliminary, are very stimulating.

There is now ample evidence that the kidneys play a major role in the causation of some cases of so-called "essential" hypertension. The physiologic studies of Smith, Rovenstine, Goldring, Chasis, and Ranges (1939) suggest that abnormal tubular function may underlie certain instances of essential hypertension. The significance of such studies is that the group of cases classed necessarily as essential is and will probably continue to grow smaller and smaller. There are at present two goals of first importance in the study of renal hypertension. The first is an understanding of the abnormality responsible for the changes in renal circulation leading to hypertension presumably through the liberation of pressor substances into the circulation. The second is the development of substances which, though not preventing the cause of the disease, can be used to counteract the pressor agents. It is hoped that the technique described above will yield additional information to help reach either or both of the two goals.

## CONCLUSIONS

1. A rise in blood pressure followed release of acute renal ischemia in 5 of 10 cats tested and in all of 7 dogs (Figs. 2, 3, and 4).
2. Pressor effects were obtained by total occlusion of the renal arteries for periods as short as three minutes.
3. Beyond the ten-minute period, greater durations of ischemia did not increase the degree or duration of the pressor response upon releasing the occluding clamps.
4. Evidence is presented suggesting that a mean arterial pressure of at least 50 to 60 mm. of mercury is necessary in order to ensure a detectable flow of blood through the kidney as tested in the above experiments.
5. Hypertension was produced by the technique described above without demonstrable effect on the stroke volume or the rate of the denervated heart in animals in which the adrenal medullae had been removed.
6. The experiments reported above are described as a convenient technique for the study of renal hypertension.

## REFERENCES

1. Alwens, W.: Experimentelle Untersuchungen über die Bedeutung der mechanischen Theorie der ... Deutsches Arch. f. klin. Med. 98: 137-163, 1909.
2. Bing, R. J.: The Formation of Hydroxytyramine by Extracts of Renal Cortex and by Perfused Kidneys, *Am. J. Physiol.* 132: 497-503, 1941.
3. Bing, R. J., and Zucker, M. B.: Formation of Pressor Amines in the Kidney, *Proc. Soc. Exper. Biol. & Med.* 46: 343-347, 1941.
4. Bingel, A., and Strauss, E.: Ueber die blutdrucksteigernde Substanz der Niere, *Deutsches Arch. f. klin. Med.* 96: 476-492, 1909.
5. Bingel, A., and Claus, R.: Weitere Untersuchungen über die Blutdrucksteigernde Substanz der Niere, *Deutsches Arch. f. klin. Med.* 100: 412-420, 1910.
6. Bright, R.: Cases and Observations Illustrative of Renal Disease Accompanied With the Secretion of Albuminous Urine, *Guy's Hosp. Rep.* 1: 338, 1836.
7. Cannon, W. B., Lewis, J. T., and Britton, S. W.: Studies on the Conditions of Activity in Endocrine Glands. XVII. A Lasting Preparation of the Denervated Heart for Detecting Internal Secretion, With Evidence for Accessory Accelerator Fibers From the Thoracic Sympathetic Chain, *Am. J. Physiol.* 77: 326-352, 1926.
8. Collins, D. A., and Hamilton, A.: Pressor Responses Following Short, Complete Renal Ischemia; Characteristics, Mechanism, Specificity for Kidney, *Am. J. Physiol.* 130: 784-790, 1940.
9. Dicker, E.: Un rein en voie d'autolyse donne naissance a des produits hypertenseurs, *Compt. rend. Soc. de biol.* 126: 88-89, 1937.
10. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: The Production of Persistent Hypertension in Dogs, *Am. J. Path.* 9: 942-945, 1933.
11. Goldblatt, H.: Experimental Hypertension Induced by Renal Ischemia, *The Harvey Lectures*, Baltimore, 1938, Williams and Wilkins Co., vol. 33, pp. 237-275.
12. Goormaghtigh, N.: Histological Changes in the Ischemic Kidney, With Especial Reference to the Juxtaglomerular Apparatus, *Am. J. Path.* 16: 409-416, 1940.
13. Grollman, A., Williams, J. R., Jr., and Harrison, T. R.: The Preparation of Renal Extracts Capable of Reducing the Blood Pressure of Animals With Experimental Renal Hypertension, *J. Biol. Chem.* (a) 131: 115-121, 1940.
14. Grollman, A., Williams, J. R., Jr., and Harrison, T. R.: Reduction of Elevated Blood Pressure by Administration of Renal Extracts, *J. A. M. A.* (b) 115: 1169-1176, 1940.

15. Katzenstein, M.: Experimenteller Beitrag zur Erkenntnis der bei Nephritis auftretenden Hypertrophie des linken Herzens, *Virehows Arch. f. path. anat.* 182: 327-337, 1905.
16. Kohlstedt, K. J., and Page, I. H.: The Liberation of Renin by Perfusion of Kidneys Following Reduction of Pulse Pressure, *J. Exper. Med.* 72: 201-216, 1940.
17. Landis, E. M., Montgomery, H., and Sparkman, D.: The Effects of Pressor Drugs and of Saline Kidney Extracts on Blood Pressure and Skin Temperature, *J. Clin. Investigation* 17: 189-206, 1938.
18. Leo, S., Prinzmetal, M., and Lewis, H. A.: Observations Upon the Pressor Substance Causing the Rise in Blood Pressure Following the Termination of Temporary, Complete Renal Ischemia, *Am. J. Physiol.* 131: 18-26, 1940.
19. Munoz, J. M., Braun-Menendez, E., Faseiolo, J. C., and Leloir, L. F.: The Mechanism of Renal Hypertension, *Am. J. M. Sc.* 200: 608-618, 1940.
20. Page, I. H.: Production of Persistent Arterial Hypertension by Cellophane Perinephritis, *J. A. M. A.* 113: 2046-2048, 1939.
21. Page, I. H.: Newer Aspects of Experimental Hypertension, Blood, Heart and Circulation, Washington, D. C., 1940, The Science Press, pp. 239-265.
22. Page, I. H., and Helmer, O. M.: A Crystalline Pressor Substance (Angiotonin) Resulting From the Reaction Between Renin and Renin-Activator, *J. Exper. Med.* 71: 29-42, 1940.
23. Page, I. H., Helmer, O. M., Kohlstedt, K. G., Fouts, P. J., and Kempf, G. F.: Reduction of Arterial Blood Pressure of Hypertensive Patients and Animals With Extracts of Kidneys, *J. Exper. Med.* 73: 7-41, 1941.
24. Prinzmetal, M., Lewis, H. A., and Leo, S. D.: The Etiology of Hypertension Due to Complete Renal Ischemia, *J. Exper. Med.* 72: 763-776, 1940.
25. Riva-Rocci, S.: Un nuovo sfigmomanometro, *Gaz. med. di Torino*, 47: 981, 1895.
26. Schroeder, H. A., and Steele, J. M.: The Behavior of Renal Blood Flow After Partial Constriction of the Renal Artery, *J. Exper. Med.* 72: 707-716, 1940.
27. Schroeder, H. A.: The Effect of Tyrosinase on Arterial Hypertension, *Science* 93: 116, 1941.
28. Smith, H. W., Goldring, W., Chasis, H., and Ranges, H. A.: Observations on the Effective Renal Blood Flow and Functional Excretory Mass in Man, With Especial Reference to Essential Hypertension, *Am. J. Physiol.* 123: 189-190, 1938.
29. Smith, H. W., Rovenstine, E. A., Goldring, W., Chasis, H., and Ranges, A.: The Effects of Spinal Anesthesia on the Circulation in Normal, Unoperated Man With Reference to the Autonomy of the Arterioles, and Especially Those of the Renal Circulation, *J. Clin. Investigation* 18: 319-341, 1939.
30. Taquini, A. C.: Liberacion de sustancia hipertensora en el rinon completamente isqueniado, *Rev. Soc. argent. de Biol.* 14: 422-428, 1938.
31. Taquini, A. C.: The Production of a Pressor Substance by the Totally Ischemic Kidney, *Am. Heart J.* 19: 513-518, 1940.
32. Tigerstedt, R., and Bergmann, P. G.: Niere und Kreislauf, *Skandinav. Arch. f. Physiol.* 8: 233-271, 1898.
33. Wakerlin, G. E., and Johnson, G. A.: Reductions in Blood Pressures of Renal Hypertensive Dogs by Hog Renin, *Proc. Soc. Exper. Biol. & Med.* 46: 104-112, 1941.
34. Williams, J. R., and Grossman, E. B.: The Recovery of an Adrenal-Like Substance From the Kidney, *Am. J. Physiol.* 123: 364-368, 1938.

## DUODENAL OBSTRUCTION

A. V. PARTIPILO, M.D., AND G. A. WILTRAKIS, M.D., CHICAGO, ILL.

*(From the Surgical Department of Loyola University School of Medicine)*

### DEFINITION OF TERMS

**D**UODENAL obstruction, in its broadest sense, may be defined as an impediment or hindrance to the forward passage of duodenal contents caused by acquired or congenital conditions. The obstruction may be acute or chronic, complete or incomplete, the characteristic feature being a dilated duodenum.

A survey of the literature concerning duodenal obstruction reveals a lamentable lack of unanimity among authors in respect to the nomenclature. The following are some of the multitudinous terms which have been applied to describe the disease: intermittent duodenal obstruction, duodenal ileus, mesenteric ileus, gastromesenteric ileus, duodenal stasis, stenosis of duodenum, megaduodenum, arteriomesenteric occlusion, dilatation and stasis of the duodenum, chronic compression of the duodenum, etc. It is obvious that these terms may be appropriately used to describe specific or individual types of obstruction; however, when used as all-inclusive titles the result is confusion, and misunderstanding arises.

Frequently, this syndrome is referred to as an ileus. The word ileus is derived from the Latin, meaning to twist. At the present time, as a result of common usage, ileus is applied to designate an obstruction due to paralytic conditions in contradistinction to that due to mechanical causes. To avoid confusion, the term ileus should be restricted to obstruction due to a disturbance in the nervous mechanism.

Mesenteric obstruction (or ileus) is a term which is most commonly applied loosely, inaccurately, and without forethought. Possibly, the reason for this is due to the fact that traction by the mesenteric pedicle is very often the cause of duodenal compression. However, other factors may be the cause, such as embryonal bands, congenital malformations, extrinsic and intrinsic tumors of the duodenum, etc. Hence, the term mesenteric obstruction does not appropriately describe the condition in all cases.

Gastromesenteric ileus, acute dilatation of the stomach, and duodenal obstruction are often used interchangeably and synonymously. This assumption is erroneous because the three conditions may occur independently. Experience has indicated to us that gastric dilatation associated with duodenal obstruction was conspicuous by its absence. We



believe that gastric dilatation and duodenal obstruction are two distinct clinical entities. For the sake of clarity the two conditions should be disassociated from each other.

Duodenal obstruction as a clinical entity is not readily understood nor generally appreciated. It is obvious that one of the reasons for this apathetic state arises from the incongruous and somewhat bounteous terms of definition. The term duodenal obstruction is self-explanatory, therefore readily understood. It is all inclusive and describes the syndrome in every case regardless of the etiological factor or its pathogenesis. Therefore we cannot be far amiss by strongly advocating the use of duodenal obstruction as the title for describing the disease, regardless of the type, in future publications on the subject.

#### ETIOLOGICAL CLASSIFICATION

Duodenal obstruction may occur at any age, afflicting male and female alike, possibly the female more often. Almost every factor in the causation of the disease has been reported. A classification of duodenal obstruction based upon etiological factors would be of material help toward a more complete understanding of the subject. Furthermore, an etiological classification has the merit of focusing attention to the fact that duodenal obstruction, as a clinical entity, is caused not only by arteriomesenteric compression, but by numerous other factors which are by far the more common causes of obstruction. These factors may be classified in two general groups: (1) those which are basically of congenital origin, and (2) those which are acquired. It is obvious that the two groups overlap in many instances. Very often the predisposing factors are acquired; whereas, the basic factor in the pathogenesis of the obstruction is of congenital origin. For instance, arteriomesenteric obstruction is in reality an accentuation of a normal condition, hence basically congenital, while the predisposing factors are usually acquired. This type of obstruction should be placed in the congenital group with the realization that it is not truly a congenital condition. Bearing these equivocations in mind, the following classification is suggested:

##### I. Congenital duodenal obstruction

- A. Arteriomesenteric (compression of duodenum by mesenteric pedicle). This type is influenced by the following predisposing factors:
  1. Ptosis of small intestine due to loss of mesenteric fat
  2. Abdominal relaxation following pregnancy and debilitating diseases
  3. Ptosis of large bowel
  4. Lordosis of lumbar spine
- B. Mesocolic. In this type of obstruction the duodenum becomes compressed by the mesocolic root alone. The condition is often associated with prolapsed hepatic flexure of the colon.
- C. Arteriomesocolic. In this type the duodenum is compressed by the mesocolic root and the middle colic vessels. It is associated with a mobile cecum and a prolapsed ascending colon and hepatic flexure.

- D. Extrinsic duodenal atresia (complete gap in duodenal continuity). The partition may be due to:
1. Arrested development
  2. Vascular changes
  3. Inflammatory effects
- E. Extrinsic duodenal occlusion
1. Anomalous mesenteric vessels occluding duodenum (Buchanan)
  2. Anomalous annular pancreas
  3. Abnormal embryonal peritoneal bands
    - a. Hepaticoduodenal (Fig. 2A)
    - b. Hepaticoduodenocolic (Fig. 2E)
    - c. Duodenoduodenal (agglutination of first upper half to second portion of duodenum). (Fig. 2D)
    - d. Duodenorenal
    - e. Jejunomesocolic (Mayo's band; also present Case 3)
  4. Contraction of ligament of Treitz, drawing duodenojejunal angle upward
  5. Faulty rotation of duodenum may produce complete or incomplete occlusion
  6. Intraperitoneal mobile duodenum
    - a. With omentum and ascending colon attached to duodenum and jejunum (Bargen and Walter's case)
    - b. With complete interruption of duodenum (Kellogg's case)
- II. Acquired duodenal obstruction
- A. Inflammatory adhesions or bands
1. Due to infection of gall bladder
  2. Essential periduodenitis of Duval
  3. Hepaticoduodenocolic bands as result of gall bladder, colonic, or gastric disease.
  4. Fixation by adhesions of transverse colon into true pelvis associated with sinking of the small intestine (present Case 2)
  5. Contracting adhesions from peptic ulcer or pancreatitis
- B. Extrinsic compression
1. Enlarged inflammatory lymph glands
  2. Lymphatic enlargement from Hodgkin's disease (present Case 5)
  3. Aneurysm of abdominal aorta (present Case 6)
  4. Kinking and angulation of duodenum following gastric operations
  5. Secondary compression of duodenum by dilated stomach (Dragstedt)
- C. Intrinsic occlusion
1. Gall bladder stones and foreign bodies
  2. Carcinoma of duodenum
  3. Intussusception due to pyloric or duodenal polyp (Kellogg)
- D. Extraduodenal
1. Jejunal dilatation due to compression at pelvic brim when small intestine is tightly wedged into pelvis (Kellogg)
  2. Jejunomesocolic inflammatory bands attaching jejunum to mesocolon

## PATHOLOGIC ANATOMY

The duodenum is from 10 to 12 inches long and extends from the pylorus to the duodenojejunal flexure. It varies from a U- to a C-shape, with the concavity of its curvature directed upward and to the left. The duodenum may be divided into four parts: (1) superior horizontal, (2) descending, (3) inferior horizontal, and (4) ascending or terminal.

The first part measures about 2 inches in length and is the direct continuation of the pylorus. It is completely surrounded by peritoneum and is rather movable. Its course is backward, to the right, and slightly upward, terminating downward into the descending portion. It forms the lower border of the foramen of Winslow and is in contact with the under surface of the left lobe of the liver and the neck of the gall bladder.

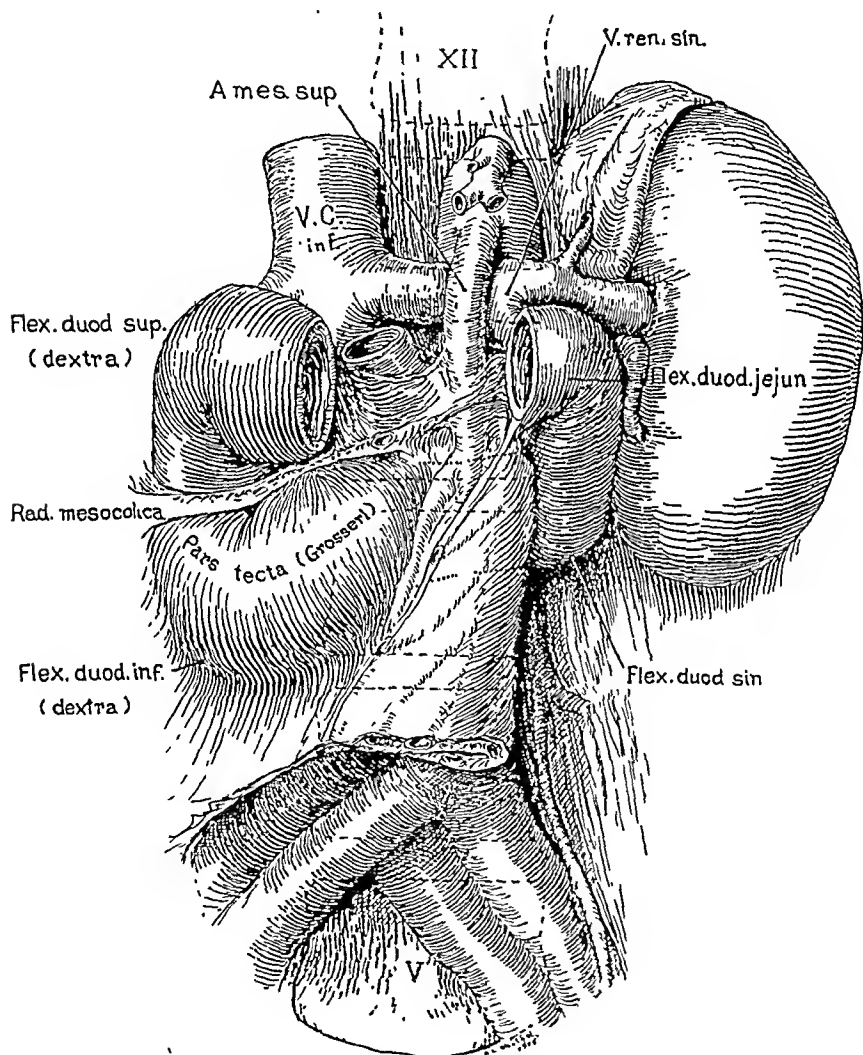


FIG. 1.—Drawing showing the topographical relationship of the duodenum, the left renal vein, and the superior mesenteric artery. (Courtesy of Dr. Bela Halpert.)

The descending portion of the duodenum is from 3 to 4 inches long. It descends along the vertebral bodies to the level of the middle of the

third lumbar vertebra, where it turns to the left and becomes continuous with the third part. It is covered by peritoneum on its anterior surface except at its middle portion where it is crossed by the root of the mesocolon. Fig. 1, taken after Halpert, is a schematic drawing illustrating the relationships of the duodenum. Note that the root of the mesocolon is shown as dividing the duodenum into an upper, supramesocolic, and a lower, inframesocolic part. This relationship is of definite clinical value as the mesocolic root may be a factor in compressing the duodenum. This is not generally appreciated nor readily understood. Bloodgood (1912) was of the opinion that this type of duodenal obstruction was due to traction on the mesenteric pedicle as a result of a dilated cecum displaced into the pelvis, and that tension on the mesentery of the small bowel could not occur unless the last portion of the ileum had an unusually short mesentery. According to Halpert (1926), "the last portion of the ileum always has a very short mesentery, or better, it never has one of any considerable length unless the cecum is movable. A displaced cecum can hardly exert sufficient tension on the mesentery of the small intestine to produce an obstruction of the duodenum, but it may do so on the mesocolon, provided that the right half of the colon has a mesocolon and is freely movable. The occlusion of this type is caused by the mesocolon and not by the mesenterium, and is therefore rather an 'arteriomesocolic' than an arteriomesenteric occlusion." He further states that, "traction on the superior mesenteric artery is also present and is exerted by the ileocolic, right colic, and middle colic arteries and not by the jejunal arteries as occurs in arteriomesenteric obstruction." In conformity with the desire to clarify the nomenclature, the term mesocolic obstruction should be applied when the compression is the result of traction by the mesocolon alone and the term arteriomesocolic when the obstruction is due to a combined traction by the mesocolon and the vessels.

Having a knowledge of the relationship of the right kidney, hepatic flexure of the colon, and the gall bladder to the first and second portions of the duodenum makes it rather easy to understand how malformations or ptosis of the kidney and colon and bands of adhesions may drag upon and distort the duodenum to produce varying degrees of obstruction. Fig. 2 illustrates various deformities of the duodenum that may result from embryonal or inflammatory bands.

The inferior horizontal part of the duodenum crosses the abdominal wall at the level of the third lumbar vertebra, from the right to the left. Its direction is slightly upward, terminating at the left of the upper part of the third lumbar vertebra. At its termination it is crossed anteriorly by the root of the mesentery of the small bowel (Fig. 1). The superior mesenteric artery, contained within the mesenteric root, springs from the abdominal aorta about  $\frac{1}{2}$  inch below the origin of the celiac artery.

opposite the first lumbar vertebra. It proceeds downward and forward anteriorly to the left renal vein and emerges from under the head of the pancreas to enter the mesentery of the small intestine. The artery accompanied by the vein continues downward, curving obliquely toward the right iliac fossa to terminate by anastomosing with one of its branches, the ileocolic artery. It is a significant anatomical fact that the superior mesenteric artery does not cross the duodenum until after it has entered the root of the mesentery. This is stressed by Halpert who states that "although the branches of the superior mesenteric artery lie between the leaves of the mesenteric fold causing the obstruction, the latter is not produced by the trunk of this vessel, nor is its site at the point where the artery leaves the aorta." If traction is applied directly on the superior mesenteric artery, the left renal vein may be compressed which may cause circulatory changes in the left kidney.

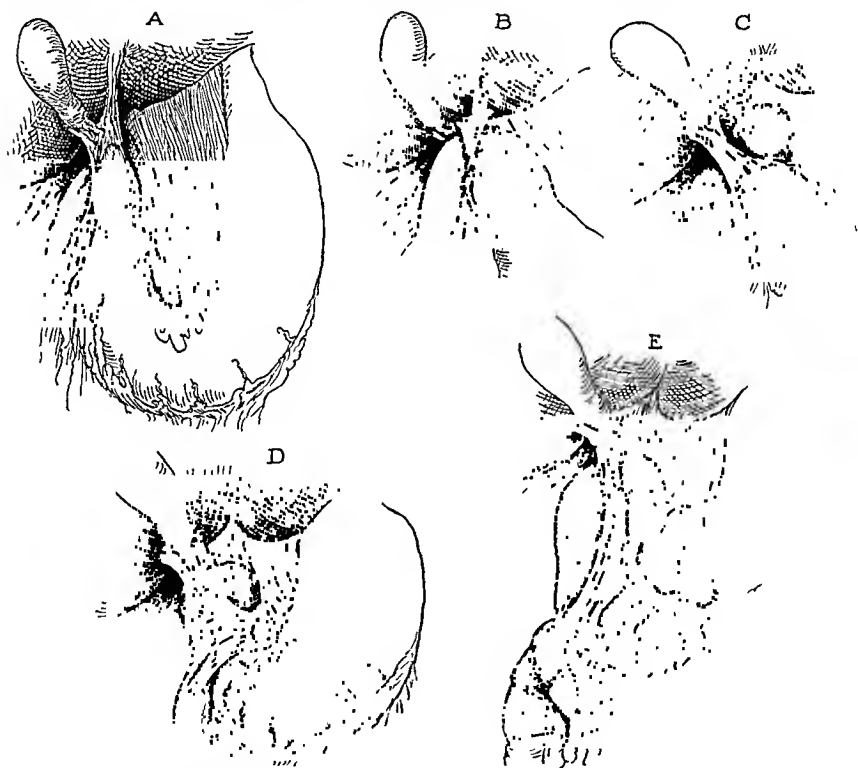


FIG. 2.—Drawing showing  
bryonal and inflammatory bar  
C. Gastroduodenobiliary. D.

In order to understand properly the pathogenesis of arteriomesenteric obstruction, one should visualize the duodenum as being located within a nutcracker with the mesenteric pedicle forming the anterior flexible half, and the aorta and spine the fixed posterior portion. Normally the

duodenum is slightly compressed, and various investigators have demonstrated a groove on its anterior surface caused by the mesenteric pedicle. According to Kellogg, the posterior surface of the duodenum also has a groove which is due to pressure of the spine alone or spine and aorta together. Hence the pathogenesis of duodenal obstruction is an exaggeration of a normal condition (Fig. 3A). Since the duodenum is relatively immobilized and the spine is unyielding, the only structure which can constrict it is the mesenteric pedicle. This occurs when a downward and backward traction is exerted on the pedicle with sufficient drag to narrow the spinomesenteric angle. Thus any condition which diminishes the space between the spine and the pedicle will do so at the expense of duodenal patency. The process is further aggravated when the spine is thrown forward, as occurs in increased lordosis of the lumbar spine. This was emphasized by Schnitzler and Vanderhoof.

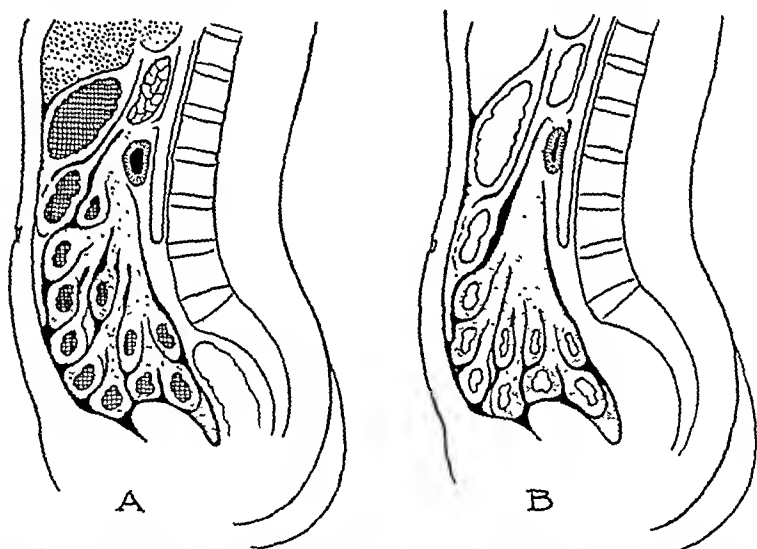


Fig. 3.—A shows the normal relationship of the spinomesenteric triangle. B. Narrowing of the triangle with compression of the duodenum as a result of loss of mesenteric fat.

There are numerous predisposing factors. We have already alluded to the ptosed colon and the drag upon the mesenteric pedicle by the vessels supplying the right half of the colon. Fig. 4 graphically illustrates duodenal dilatation resulting from traction by the middle colic artery, following ptosis of the right half of the colon and the hepatic flexure. Normally the small intestine is retained within the abdomen proper by the mesenteric fat; however, when there is an appreciable loss of this fat, the intestine loses its support and sinks into the lower abdomen and even into the true pelvis (Fig. 3B). As a consequence there is a downward and backward traction on the mesenteric pedicle, thus narrowing the spinomesenteric angle, with the result that the duodenum becomes

compressed. Similarly, since the small intestine is suspended in a vertical position from the posterior body wall, a relaxation of the abdominal wall facilitates the prolapse of the small intestine. Therefore, frequent pregnancies, or any factor which augments abdominal relaxation, aggravates the condition. This is further aggravated in the female because all the diameters of the pelvis are increased. The greater incidence of visceroptosis in the female is probably due to this factor.

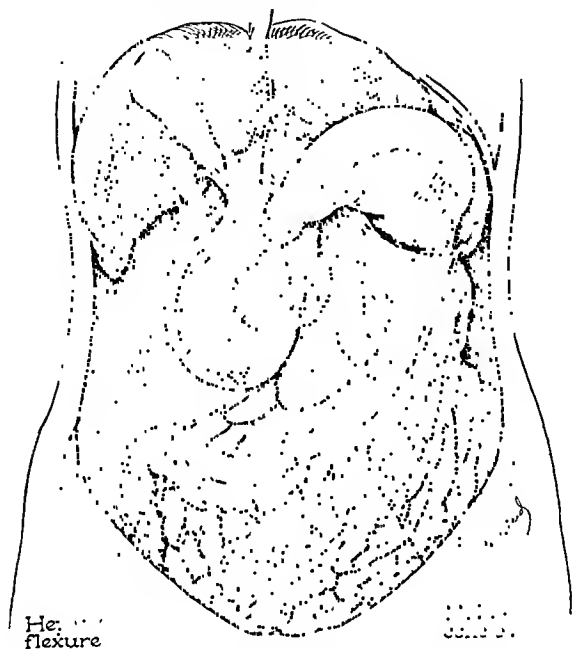


Fig. 4.—Duodenal dilatation due to traction by the middle colic artery as a result of ptosis of the ascending colon and hepatic flexure.

While traction on the mesenteric pedicle is the most common cause of compression, the terminal duodenum may also become constricted by the middle colic artery as a result of a prolapsed transverse colon. This occurred in one of the cases herein reported. The middle colic artery arises from the front of the superior mesenteric artery just before the latter enters the root of the mesentery of the small intestine. In our case, the transverse colon was firmly adherent by adhesions to the true pelvis, dragging the middle colic artery vertically downward and backward in the same plane as the mesenteric pedicle of the small intestine. The duodenum was found greatly distended, and we believe that its compression was due to the traction by the middle colic artery, and not by the mesenteric pedicle. Nevertheless, it is possible that the middle colic artery may have arisen from the superior mesenteric after the latter artery crossed the duodenum. In such contingency the compression

would be due to traction on the mesenteric pedicle by the middle colic artery. This is only of academic interest, because in either exigency the treatment is the same.

There is considerable controversy concerning the pathogenesis of acute gastric dilatation. Two theories have been proposed: (1) that the dilatation is primarily a reflex nervous disturbance; (2) that dilatation of the stomach is associated with, or is secondary to, arteriomesenteric obstruction. Kellogg (1935) recognized the possibility of acute gastric dilatation, but believed that in the majority of instances mesen-

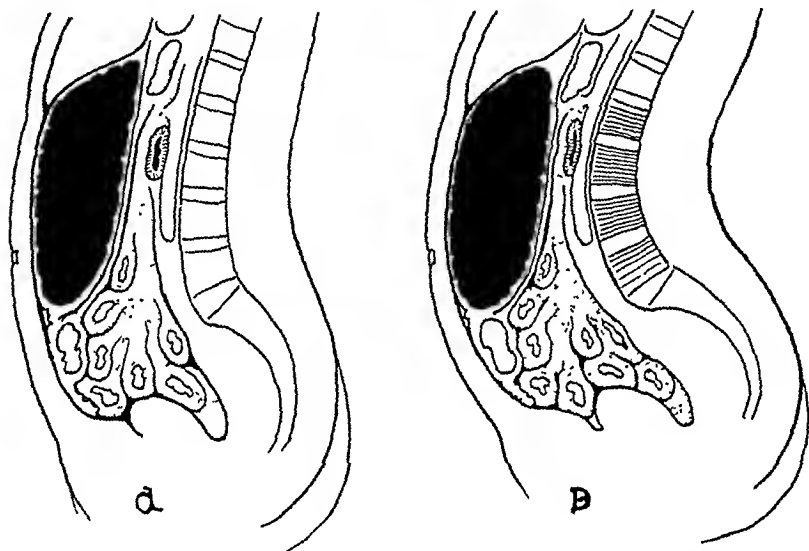


Fig. 5.—A, illustrates how dilatation of the stomach forces the small intestines into the pelvis, produces a downward and backward traction on the mesentery, and B a secondary duodenal compression (after Dragstedt and co-workers).

teric obstruction was also found. He thought that the essential pathology was compression of the third part of the duodenum by the mesenteric pedicle. He stated that gastric dilatation may also be produced by kinks at the superior and duodenal-jejunal angles, and occasionally by compression of the jejunum at the pelvic brim when the small intestines are tightly wedged into the pelvis. On the other hand, Dragstedt, Montgomery, Ellis, and Matthews, in an excellent study of the subject concluded that gastric dilatation following operation was due to a reflex inhibition of the peripheral gastric motor mechanism through impulses reaching the stomach by way of the vagi and splanchnics. They believed that an enlarged duodenum, if present, was secondary, and was caused either by a direct pressure of the dilated stomach on the transverse duodenum, or by a secondary arteriomesenteric compression brought about by the downward pressure of the dilated stomach which forced the intestine into the pelvis (Fig. 5).



While not wishing to become involved in this controversy, nevertheless, it is our opinion that the proponents of these theories are at cross purposes. It is universally agreed that acute gastric dilatation is most frequently seen as a postoperative complication and seldom as a consequence of arteriomesenteric obstruction. In none of the cases of primary acute duodenal obstruction did we observe a grossly dilated stomach. This is also the experience of others. This significant observation must be taken into consideration when discussing the pathogenesis of acute gastric dilatation. Since gastric dilatation is an uncommon sequela of arteriomesenteric obstruction, it is logical to conclude

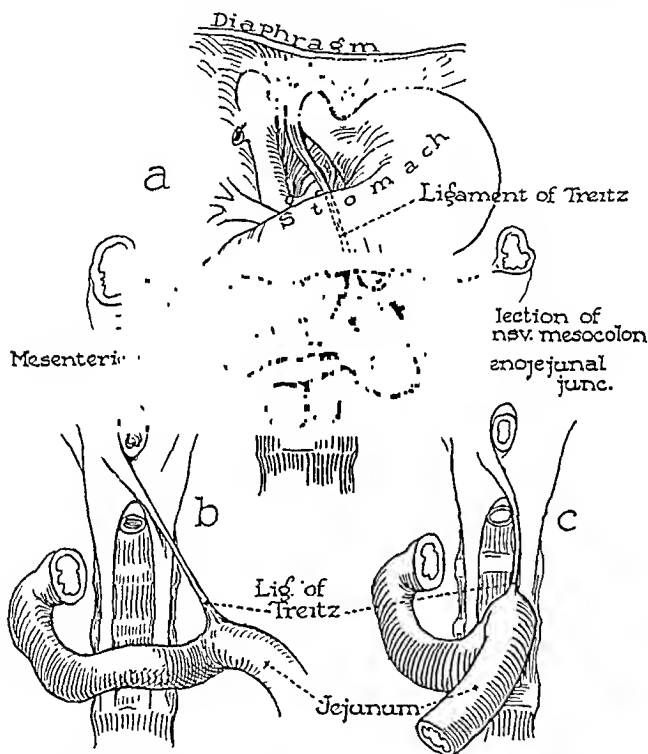


Fig. 6.—A. Schematic representation of the duodenum and its relationship. B. Elongated ligament of Treitz. C. Short ligament which draws the duodenojejunal flexure rather high and to the left, thus rendering the flexure more acute.

that its causative factor must be looked for elsewhere, possibly in the stomach as suggested by Dragstedt and his co-workers. On the other hand, it must be conceded that when the duodenum is coincidentally enlarged with the stomach the phenomenon is most likely and primarily of arteriomesenteric origin, and not secondary to the pressure of a dilated stomach. Thus there are two distinct clinical entities: (1) postoperative acute gastric dilatation due to a disturbance in the gastric nervous innervation and not accompanied by a duodenal dilatation,

the most common type; (2) gastromesenteric obstruction, an uncommon postoperative complication and its causative factor is primarily in the duodenum. If these terms are properly applied, a great deal of confusion and misunderstanding will be obviated.

Duodenal obstruction not infrequently occurs as a result of an acute angulation of the duodenojejunal flexure. Its pathogenesis is based upon a disturbance of the normal relationship of the duodenum and the ligament of Treitz. When the terminal duodenum reaches the left side of the first or second lumbar vertebra, it turns abruptly forward, downward, to the left, and passes into the jejunum. This bend, known as the duodenojejunal flexure, is fixed by a thin band of unstriped muscle called the ligament of Treitz. The latter is attached to the left crus of the diaphragm, and is continuous with the duodenal musculature. Its relative length determines the position of the duodenojejunal flexure. If short, the flexure is placed rather high and to the left, thus rendering the flexure more acute (Fig. 6C). The acuteness of the angulation may be accentuated by a gastrojejunostomy, especially when the patient is in Fowler's or semisitting position. For this reason the surgeon should examine the duodenojejunal flexure in all cases when a posterior gastrojejunostomy is contemplated. If found acutely angulated, the ligament should be divided and its end ligated.

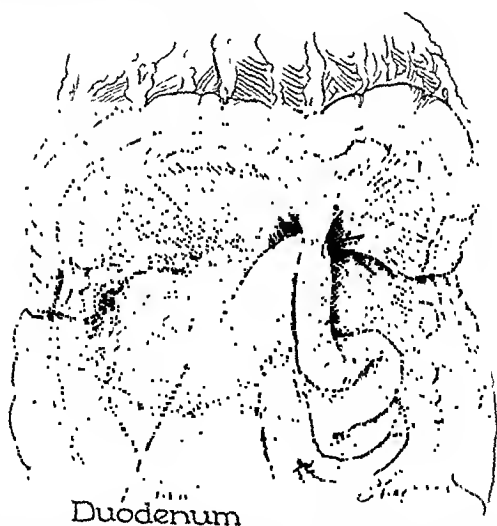


Fig. 7.—Mayo's band. The first portion of the jejunum is fixed to the inferior surface of the mesocolon, thus acutely angulating the duodenojejunal flexure by pulling the jejunum to the right of the body.

Duodenal obstruction may also result from an abnormal attachment of the first loop of jejunum to either the transverse colon or mesocolon. In 1908 Mayo described the attachment of the first loop of jejunum to the transverse mesocolon by bands of adhesions. As illustrated in Fig. 7,

this band unites the inferior surface of the mesocolon to the anterior surface (right side) of the jejunum, thus pulling the jejunum to the right side and acutely angulating the duodenal jejunal angle. A very unusual abnormality of the first loop of jejunum was observed in Case 3. As illustrated in Fig. 8, about 3 inches of the jejunum was firmly attached to the transverse mesocolon by a peritoneal band. Kellogg described a case of duodenal obstruction due to compression of the jejunum at the pelvic brim as a result of the small intestine's being tightly wedged into the pelvis.



Fig. 8.—About 3 inches of the jejunum are attached to the transverse mesocolon by an embryonal peritoneal band (Case 3).

#### DIAGNOSIS

The diagnosis of duodenal obstruction may be easily arrived at in some cases, while in others it may not be so obvious. The first requirement for a diagnosis is a thorough knowledge and familiarity with the subject, and the utilization of this knowledge in the differential diagnosis of all obscure upper abdominal diseases. The duodenum has been called the silent portion of the gastrointestinal tract, however, it will speak loudly if attention is paid to it. No single symptom or combination of symptoms and physical findings is pathognomonic. However, when these symptoms and findings are analyzed in conjunction with the history of the case, and supplemented with roentgen studies, they assume definite characteristics indicative of duodenal obstruction.

The history of chronic duodenal obstruction reveals that the age group is in the third decade, and that it occurs more often in the female than in the male (ratio variably given as 3:1). These patients are the visceroprotic type; asthenic, undernourished, thin individuals with

seaphoid abdomens. A great majority of them have had previous medical treatment for "stomach trouble," peptic ulcer, gall bladder disease, chronic appendicitis, dyspepsia, "nervous stomach," "vagotonia," neurasthenia, or other chronic abdominal ailments. Many will give a history of having had one or more laparotomies, which not only failed to relieve them but very often aggravated the original symptoms. The physician should be on the alert and investigate the duodenum when a patient gives a history of being treated for neurasthenia, gastric neurosis, or dyspepsia. It is our belief that the underlying cause of neurasthenia in some cases is due to an obscure disturbance of one of the body systems, such as the reproductive, endocrine, genitourinary, gastric, etc. If a neurasthenic patient presents gastric symptoms, it seems logical to us that duodenal pathology should be ruled out.

Patients with chronic duodenal obstruction involving the first or second portion of the duodenum may be well developed and do not present the physical characteristics of the asthenic type. Their symptoms usually are wrongly diagnosed as peptic ulcer or chronic gall bladder disease. Very often it is difficult to make a differential diagnosis as the symptoms of chronic obstruction affecting the first and second portion of the duodenum are similar to these conditions. However, two important facts stand out: (1) medical treatment for peptic ulcer or for the gall bladder disease fails to relieve the symptoms, and (2) roentgen studies invariably reveal a duodenal deformity.

A host of symptoms descriptive of duodenal obstruction have been enumerated by various writers. The following is a more or less comprehensive list: vomiting, nausea, bilious attacks, migraine headache, constipation, loss of weight, eructation, epigastric pain, regurgitation, borborygmus, dragging sensation, etc. One can readily see that these symptoms taken singly or collectively are suggestive of any number of abdominal diseases, and not conclusive of any. However, when analyzed in relation to the duration of the illness, onset and course, and correlated with physical and x-ray findings, they assume certain features characteristic of duodenal obstruction, and become distinguishable from other abdominal conditions.

The history reveals that in chronic duodenal obstruction the illness is of long duration. Many patients will date back their complaints since childhood. The diagnosis of chronic duodenal obstruction in one of our patients (Case 3), who was referred to us with a diagnosis of perforating and bleeding ulcer, was made because the patient stated that he had had gastric distress since he was 6 years old. This was the only clue which, coupled with subsequent roentgen findings, indubitably revealed the cause for the long-drawn-out history of gastric distress. The operative findings revealed a duodenal obstruction due to fixation of the first loop of jejunum to the transverse mesocolon in addition to the ulcer complications.

Another characteristic feature of the chronic type is the intermittent recurrent attacks. In some individuals these attacks may be in the nature of "gastric disturbances," such as constipation, nausea, headache, and "bilious attacks," while in others they may be ushered in with nausea, vomiting, epigastric pain, and other symptoms indicative of a high intestinal obstruction. In some individuals the attacks may not be particularly severe until early adult life. In such cases the acute attack is probably brought on as a result of abdominal relaxation following frequent pregnancies, or loss of mesenteric fat following a debilitating disease. It should be stressed at this time that acute duodenal obstruction ushered in without a history of previous attacks is usually due to occlusion of the duodenum by extrinsic or intrinsic tumor.

Of the symptoms enumerated, vomiting is the most characteristic. It is generally intermittent and the vomitus contains enormous quantities of bile. When the obstruction is complete, the emesis is abundant, continuous, and occurs soon after a meal is eaten. The attack may last twenty-four hours or longer depending upon the degree of obstruction. In one of our cases (Case 1) the patient vomited for a period of nine days, and was relieved only after a duodenojejunostomy was performed. At times, vomiting will be relieved by assuming the knee-chest position, or by lying on the abdomen or the right side. This is a significant factor to elicit in the history since it is only in duodenal obstruction that posture will relieve the patient of vomiting. In Case 2, the patient stopped vomiting while resting in bed with the foot elevated 18 inches. This was used as a therapeutic test. Subsequent x-ray examination confirmed the diagnosis. This test is not always positive as elevation of the foot of the bed may not always relieve the compression of the duodenum.

Epigastric pain is associated with vomiting. It varies from a mild discomfort to a sharp colicky pain. The patient is relieved or the pain subsides after vomiting. The pain in duodenal obstruction is probably due to the distended duodenum and to the unyielding spastic pylorus. When the pylorus yields, the duodenal contents empty into the stomach and the patient vomits. Thus relief of pain which follows is possibly the result of pyloric relaxation and relief of intraduodenal pressure. The process is a vicious circle as the pain will recur with subsequent accumulation of secretion in the duodenum. In some cases vomiting may not be a prominent feature; however, examination of gastric contents will reveal large quantities of bile.

#### X-RAY EXAMINATION

Careful roentgen studies will confirm the diagnosis in practically every case. It should be noted, however, that if these studies are made in between the acute attacks, when the patient is free from symptoms, the roentgen observations may be negative. Roentgen observations were

first reported by Jordan in 1911, who described and showed by x-ray plates the findings of duodenal obstruction. These findings were verified by Lane. Jewett, quoted by Liehty, insisted that certain essential points are necessary to establish the diagnosis. He said: "The essential points then are dilatation of the duodenum, writhing of the duodenum, waves of reverse peristalsis, puddling at the duodenal junction. There is usually a low descending loop in the duodenum and a high point of fixation of the duodenojejunal angle which can be demonstrated by lifting of the stomach. There is often a six-hour gastric stasis, and the duodenal cap is not infrequently dilated along with the rest of the duodenum. The diagnosis, however, is made largely on the fluoroscopic findings."

Kellogg and Kellogg, in 1927, noted that changes in the duodenum follow one of four types:

1. Asthenic duodenum (symptoms latent or toxic). Roentgen examination may show delay or puddling in the duodenum, with sluggish peristalsis and slight or no dilatation.

2. Duodenal obstruction, with incompetent pylorus. Bile regurgitates easily into the stomach. Dilatation is usually moderate or absent. Roentgen-ray examination is negative or shows reverse peristalsis.

3. Obstruction, with hypertrophy (the writhing duodenum). The duodenum is elongated and its walls are thickened. Under the fluoroscope it is seen to labor over its contents.

4. Dilated duodenum. The area of duodenal tympany is increased; succussion is present. Pain occurs, either steady and dull or cramp-like. This variety is most readily demonstrated by the roentgenologist.

Shattuck and Imboden have made the following observations:

1. Bands about the first and second portion of the duodenum may show the duodenum markedly contracted in size in comparison with the size of the stomach, or it may be larger than normal. The duodenum may be deformed, as in ulcer, but the deformity is not constant and varies from time to time in various positions.

2. The upper part of the descending limb may be fixed, and the part adjacent to the liver may have a flattened appearance, thus obliterating the normal curvature of the duodenum.

3. A commonly observed phenomena is a fixation of the dependent limb of the duodenum to the liver at a certain point, producing a definite angulation.

4. Obstruction at the ligament of Treitz shows the angle is shifted to the right of its normal position. The dependent duodenum is usually enlarged, especially in its transverse diameter, and the valvulae conniventes are frequently absent.

To summarize, the findings and technique of fluoroscopic examination are: The examination is made while the patient is standing. After the stomach has been examined, it is pushed upward and to the left by the examiner's hand, thus gaining an unobstructed view of the duodenum.

Barium will be seen to enter the duodenum rather rapidly at first; however, as soon as it reaches the lumbar vertebrae, it stops. The duodenum becomes filled and is seen to enlarge. Soon the barium from the stomach stops flowing into the duodenum, and instead, as a result of an active antiperistalsis, there is regurgitation of the duodenal contents into the stomach. The duodenum may appear to be contorted or writhing, and the contents may be seen to sway back and forth in churning movements. A five-hour plate will invariably reveal duodenal and gastric residue and a dilated duodenum.

Disappearance of these findings by Hayes' maneuver is confirmatory. The Hayes' maneuver is as follows: Pressure is made by the hand over the abdomen just below the umbilicus. The mass of intestine is pushed upward, backward, and to the left, thus relieving the downward and backward traction on the mesenteric pedicle. In about thirty seconds the duodenojejunal angle is opened and the duodenal contents are seen to pass into the jejunum. The descending portion of the duodenum may be visualized in the lateral view.

#### TREATMENT

The treatment of duodenal obstruction depends to a great extent upon the underlying causative factor. The treatment for the viscerotonic type and for the chronic form of duodenal obstruction is preferably medical. The objective is to increase the fat content of the mesentery in order to elevate the small intestine upward and forward, thereby relieving the backward and downward traction on the duodenum by the mesenteric pedicle. This can be accomplished by postural rest in bed, high caloric fat diet, and abdominal exercises. Having the patient rest in bed, the foot of which is elevated 12 to 18 inches, permits the small intestine to migrate into its normal position. The pressure on the duodenum is materially relieved by having the patient lie on the abdomen as much of the time as possible, especially immediately after each meal (at least twenty minutes). The abdominal muscles are strengthened by abdominal massage, setting-up exercises, and alternate raising of the legs at right angles with the body in the prone position. In the beginning these exercises must be done with moderation, and at no time must they tire the patient. At the same time the patient is placed on a nourishing diet. During the first few days the food intake should contain about 1,800 calories, and later should be increased to a minimum of 3,000 calories. The major portion of the foods should contain high caloric values in fats and carbohydrates, such as vegetables, fruits, cereals, fish, milk, cream, farinaceous puddings, butter, etc. The food should be thoroughly cooked, and small frequent feedings are preferable to the usual three meals a day.

The majority of these patients are constipated, hence every effort should be directed to control normal bowel movements. Strong laxatives

or purgatives should be avoided as they only aggravate the condition. Judicious use of mineral oil or milk of magnesia has been found to be serviceable in our experience. As long as the patient is resting in bed 1 tablespoonful of milk of magnesia is given three times a day until the number of bowel movements are abnormally increased, when the amount of magnesia is decreased to produce a normal desired effect.

Postural rest in bed, judicious exercises, and intelligent use of a high-calorie diet prolonged for a period of months will bring about relief in the great majority of patients. If satisfactory results are not obtained, surgical intervention is indicated. The following criteria may be used to decide the question of operation: (1) failure of medical treatment to relieve the symptoms after a prolonged fair trial; (2) inability of the patient to gain weight after three months of postural and medical management; (3) duodenal retention as shown by a five-hour x-ray plate; (4) persistency of vomiting during medical treatment; and (5) recurrent attacks of vomiting.

For the mesenteric type of obstruction the operation of choice is a duodenojejunostomy. This is the only procedure which adequately and thoroughly drains the obstructed duodenum. Some authors have suggested a gastrojejunostomy; however, it must be recognized that this operation does not adequately drain the obstructed duodenum. It relieves the patient temporarily by short-circuiting the gastric contents, but the duodenal contents are not emptied, and as a result, the patient may continue to complain of the original symptoms. A gastrojejunostomy may even aggravate the condition by increasing the duodenojejunal angle, thus complicating the mesenteric obstruction. We agree with Wolfer (1927) that suspension of the ptosed viscera is uniformly unsuccessful for the cure of arteriomesenteric obstruction.

When the cause of the obstruction is an inflammatory or embryonal band, simple division of the band is the procedure of choice. Denuded surfaces must be peritonized by either an omental graft or by suturing, else the condition is apt to recur. Gastrojejunostomy or better, gastroduodenostomy is the logical procedure in those cases with massive adhesions involving the first portion of the duodenum.

Colopexy, after the technique of Waugh, or colofixation to the anterior abdominal wall is the operation of choice for the mesocolic and arteriomesocolic obstruction. For the arteriomesocolic type, a duodenojejunostomy is a logical supplemental procedure, as colopexy or colofixation alone may not completely relieve the compression. Right colectomy as suggested and performed by Bloodgood is too formidable and should be replaced by a more conservative and less dangerous procedure.

The treatment of carcinoma of the duodenum, when the growth is removable, is resection with an end-to-end anastomosis to re-establish the lumen continuity. If the growth is fixed or invasive, or if metastases are present, a duodenojejunostomy is indicated.



## CASE REPORTS

**CASE 1.**—Sister M. C., aged 31 years, was admitted to the St. Mary of Nazareth Hospital on June 27, 1937. The chief complaints were vomiting for one month, epigastric pain of two months' duration, nausea, and loss of 13 pounds in weight within the past two months. The pain was localized in the upper right quadrant. At the onset, about two months before, it was mild and associated with nausea; however, within five weeks it had become more severe, nausea increased in proportion, and soon the patient vomited a green-colored fluid which brought about relief of pain. The attacks of pain occurred about one-half hour after eating. Upon admittance the patient's chief complaint was vomiting. The vomitus was deeply bile stained and contained food or fluid taken previous to vomiting. On July 1 one of us (A. V. P.) was called into consultation and the following observations were made: The patient stated that she could not take anything by mouth without vomiting it. The pain was not particularly severe. Vomiting occurred at about five to ten minutes following intake of food or fluid. The epigastric region was slightly distended and tympanitic, and no rigidity was elicited. The patient was rather weak and dehydrated. Past history revealed that the patient had had an appendectomy in 1929 and a thyroidectomy in 1932.

**X-ray Report.**—Roentgen examination of the stomach showed ptosis of the stomach with the greater curvature extending 5 inches below the umbilicus. The stomach had some difficulty in emptying, and a reverse regurgitation of the duodenal contents was noted. The duodenum was enlarged, and barium passed into the jejunum with difficulty and at irregular intervals.

**Operation.**—Duodenojejunostomy was performed on July 3.

**Comment.**—The operative findings revealed the stomach free from ulcers or tumors. Upon lifting the transverse colon the retroduodenum was seen bulging through the mesocolon. It was dilated to about twice its normal size. The small intestine was found collapsed and its mesentery wanting in fat. Lifting of the mesenteric pedicle caused the duodenum to empty into the jejunum. This patient was of the asthenic, thin, visceroprotic type. The cause of the obstruction was apparently due to the absence of mesenteric fat. The patient made an uneventful recovery.

**CASE 2.**—Megaduodenum due to adherent transverse colon into the pelvis. Mrs. T. F., aged 35 years, was admitted to the Elgin State Hospital on March 2, 1937. She had had abdominal pain for a period of two years. The pain was "cramp like" in nature, diffusely distributed over the abdomen, but more marked in the epigastrium, and was associated with recurrent attacks of vomiting. In December, 1936, she had been treated for peptic ulcer at the Cook County Hospital.

She entered the Elgin State Hospital for observation. Upon admittance she showed no overt psychotic manifestations. Her chief complaint was vomiting which occurred at irregular intervals, and epigastric pain was associated with food intake. The pain and vomiting ceased while the patient remained in bed. Past history and physical findings: oophorectomy, 1914; appendectomy, 1918; removal of lingual tumor, 1930. Physical examination revealed a well developed, white female lying comfortably in bed, not appearing acutely ill. Temperature varied from 99 to 100.8°; pulse varied between 80 and 96; blood pressure, 124/86; right McBurney and suprapubic scars on the abdomen; tenderness elicited in epigastrium and upper

quadrants; no muscular rigidity; the ascending colon was tympanitic. Physical findings elsewhere were essentially negative. Serology, blood chemistry, gastric and urine analyses were negative.

*X-ray Findings.*—The stomach was low in the pelvis. There was a marked dilatation of the first, second, and the beginning of the third portions of the duodenum with reverse peristalsis present. Very sharply demarked limitation of the passage of barium at the midportion of the third part of the duodenum in the region of the spine. The stomach filled readily and rugae were present. The duodenal cap was clearly visualized and smooth in outline. An immediate plate (Fig. 9) revealed the descending and transverse portion of the third part of the duodenum was markedly dilated, measuring about 3 inches in diameter, and sharply terminating over the spine. A six-hour plate (Fig. 10) revealed 60 per cent of gastric residue, with barium remaining in the duodenum and duodenal cap, and some barium present in the terminal portion of the ileum and ascending colon. A twenty-four hour plate revealed a small amount of barium scattered in the ascending, transverse, and sigmoid colon.



Fig 9—Case 2 Compression of the duodenum by the middle colic artery. Immediate plate showing the markedly dilated duodenum which is sharply terminated over the spine

*Operative Findings.*—The patient was operated upon on March 19, 1937, seventeen days after admission. Upon opening the abdomen numerous adhesions were encountered. The transverse colon was adherent firmly into the true pelvis by adhesions. There was considerable drag upon the mesocolon. The stomach was slightly dilated; its wall was thin, and the pyloric sphincter admitted two fingers. There was no evidence of ulcers or scars in the stomach wall. Upon lifting the right half of the transverse, the retroduodenum was seen bulging through the mesocolon, and the diameter of the duodenum was estimated to be about 4 inches. The first portion of the jejunum was empty and of normal size; however, its wall appeared to be edematous.

*Operative Procedure.*—An attempt was made to free the transverse colon from the pelvis, but it was so densely attached that this was impossible. A duodeno-jejunostomy was done between the collapsed jejunum and the dilated retroduodenum.

*Follow-Up Notes.*—The patient made an uneventful recovery. On April 28, 1937, the fortieth postoperative day, x-ray studies were made. An immediate plate (Fig. 11) revealed the barium passing directly from the duodenum into the jejunum through the new opening. The six-hour plate (Fig. 12) revealed the stomach empty, and most of the barium in the colon. On May 21, 1937, the patient was discharged from the Elgin State Hospital with the following notation: "Patient gained 20 pounds in weight since her operation. She has been discharged from the institution as without psychosis, and having recovered from the acute physical condition."



FIG. 10.—Case 2. Compression of the duodenum by the middle colic artery. Six-hour plate shows 60 per cent residue in the stomach, with barium in the duodenum and duodenal cap.

*Comment.*—This case illustrates the importance of examining the duodenum in all cases of unexplainable gastric symptoms. X-ray findings, before and after operation, the operative findings, and the complete relief of symptoms following the operation are conclusive evidences that in this case the symptoms were due to a duodenal obstruction, and not the result of peptic ulcer or of a neurasthenic syndrome.

The obstruction was due to the downward and backward pull of the middle colic artery on the duodenum, and not mesenteric traction. The operation of choice would have been a colopexy; however, this was not possible because of the firmly attached transverse colon in the pelvis.

CASE 3.—Embryonal band attaching the first loop of jejunum to the transverse mesocolon associated with bleeding and perforating peptic gastric ulcer. Mr. E. L.,



Fig. 11.—Case 2. Compression of the duodenum by the middle colic artery. Immediate plate made on the fortieth postoperative day. Note the barium passing directly into the jejunum through the duodenojejunostomy.



Fig. 12 —Case 2. Compression of the duodenum by the middle colic artery. Six-hour plate, fortieth postoperative day, shows the stomach empty and that the barium has reached the colon.

aged 41 years, a farmer. Since 6 years of age the patient has experienced abdominal distress characterized by nausea, abdominal pain, and vomiting. The pain was located in the epigastrium, was relieved by vomiting, and was not related to food intake. In 1922 a diagnosis of bleeding peptic ulcer was made and he received medication which gave him relief. He was then free from symptoms for about fifteen years. In June, 1935, he had a severe gastric hemorrhage which came on suddenly without previous pain or warning. He was treated medically, about two months being required for complete recovery. In December he began having epigastric pain which was often, but not constantly, relieved by vomiting. Pain upon admittance was dull, extended across the hypochondriac regions, and not related in time to eating. Within the past two weeks he had vomited every day. During the past week his stools had been black and associated with marked constipation. The vomitus was sometimes almost all liquid, brown or greenish in color, but not "coffee-ground" in appearance. The patient was referred to one of us (A. V. P.) with a diagnosis of bleeding and perforating gastric ulcer, as substantiated by x-ray studies.

Physical examination was essentially negative except for some tenderness and slight rigidity in the epigastrium.

*Laboratory Tests.*—R. B. C., 3,870,000; hemoglobin, 64.9; total protein plasma, 5.85; urine, negative; fractional meal analysis, lowest free HCl, 31 degrees, highest 75 degrees; Kahn test, negative; stool examination showed occult blood, 1 plus.

*X-ray Examination.*—The following report was given on the x-ray examination made upon admittance at Mercy Hospital:

"The fluoroscopic examination made with the radiopaque medium revealed the emulsion entering the esophagus freely and dilated it normally. There was no evidence of lagging at the cardia. The stomach filled readily with the greater curvature reaching the level of the crest of the ilium in the median line. Peristaltic function was hyperactive with the waves not closing off accurately to the tip due to effects on the lesser and greater curvature of the pylorus at the antrum. The first portion of the duodenum showed a diverticulum in the inferior surface, and several defects on the superior surface. The second portion of the duodenum showed the barium passing through it, without any evidence of peristalsis, in a thin stream. The proximal end of the third portion of the duodenum was markedly dilated, and anti peristalsis was very evident. Patient complained of tenderness upon palpation over the defects.

"The five hour roentgenogram showed some retention of the barium in the diverticulum, and the remainder of the barium distributed throughout the colon."

*Preoperative Diagnosis.*—Bleeding and chronic perforation ulcer; chronic duodenal obstruction due to an embryonal band fixing the first loop of jejunum; possible gastroduodenal fistula

*Operative Findings.*—There was a stellate scar on the anterior surface of the pylorus. The pyloric end of the stomach and the first part of the duodenum were firmly adherent together, and apparently a fistulous tract communicated between them. The head of the pancreas was slightly enlarged. The first loop of jejunum was found adherent to the transverse mesocolon, and its direction was to the right of the body (Fig. 8).

*Procedure.*—The embryonal band was excised, and the first loop of jejunum restored to its normal position. A partial gastrectomy was performed.

#### *Pathologic Report.*—

"Specimen consists of a pyloric segment of the stomach measuring 14 cm. in length. Peritoneum covering what is apparently the anterior surface of the stomach is smooth and reddish gray in color. That covering which is apparently the posterior aspect seems roughened by torn fibrous adhesions. The mucosa is swollen, reddish

tan in color, and on it red-stained mucous is noted. About 4.5 cm. proximal to the pylorus is apparently a small out-pouching of the wall. This is lined by smooth, reddish tan mucosa. Along the margin of this out-pouching a small depressed area about 4 mm. in diameter is noted. Microscopic diagnosis: subacute perforating peptic ulcer, located at pylorus."

*Comment.*—The patient made an uneventful recovery, and at this writing, one year after operation, he is free of all symptoms. This case illustrates the importance of investigating the duodenum when a history of gastric distress dates from childhood.

CASE 4.—Mrs. E. N., aged 64 years. Duodenal obstruction due to carcinoma of the terminal duodenum. The patient was admitted to the Grant Hospital on Aug. 13, 1938, with the history of two previous admittances to the hospital. At first admittance, May 4, 1938, the patient's chief complaint was vomiting. After three days of observation she was discharged with a diagnosis of chronic cholecystitis. Two months later, July 18, 1938, the patient was readmitted, and the following history was obtained: intermittent attacks of vomiting, pain in the upper right quadrant, and some distention of the abdomen. The vomitus was bile-stained. She appeared dehydrated and acutely ill. X-ray examination was made at this time with the following report:

"Esophagus, stomach, and duodenal bulb negative fluoroscopically and radiographically, but the barium nevertheless was held up in the bulb in the erect position and only went through while lying down. There was a small retention in the bulb at the five-hour examination [Fig. 13]. This we believed to be due not to duodenal pathology but to pressure and adhesions from adjoining gall bladder. Gall bladder: suspicion of gall bladder pathology verified by the fact that the gall bladder was not well visualized, but nevertheless, was outlined sufficiently showing it to be distinctly enlarged and undoubtedly pathologic. At the same time some of the dye remained in the stomach, again verifying partial obstruction in the duodenum."

The patient was operated upon on July 26, 1938, and the gall bladder removed. She continued to vomit postoperatively and on Aug. 5, 1938, she was discharged as having improved.

The patient continued to vomit greenish fluid, and on Aug. 13, 1938, she was readmitted. At this time one of us (A. V. P.) was called into consultation. Examination revealed that the patient was extremely dehydrated, weak, and unable to retain anything in her stomach. The abdomen was distended and tender. The temperature was 102°. After examining the x-ray plates (Fig. 13) that were taken during her previous admission, a diagnosis of acute duodenal obstruction was made, and an operation was advised.

*Operative Findings.*—The stomach was slightly dilated and somewhat edematous. The pylorus and the hepatic flexure of the transverse colon were adherent to the anterior parietal peritoneum. A tumor about the size of an orange was found to involve the terminal portion of the duodenum. It was hard and rather vascular. There were lymphatic enlargements along the mesentery of the small intestine. Exploration of the pelvic organs, large bowel, and elsewhere in the abdomen failed to reveal any tumefaction. A duodenojejunostomy was performed. The patient died two days later. Unfortunately permission to perform an autopsy could not be obtained.

*Comment.*—Since the onset of the patient's illness the chief complaint had been vomiting of greenish material. The vomiting became

aged 41 years, a farmer. Since 6 years of age the patient has experienced abdominal distress characterized by nausea, abdominal pain, and vomiting. The pain was located in the epigastrium, was relieved by vomiting, and was not related to food intake. In 1922 a diagnosis of bleeding peptic ulcer was made and he received medication which gave him relief. He was then free from symptoms for about fifteen years. In June, 1938, he had a severe gastric hemorrhage which came on suddenly without previous pain or warning. He was treated medically, about two months being required for complete recovery. In December he began having epigastric pain which was often, but not constantly, relieved by vomiting. Pain upon admittance was dull, extended across the hypochondriac regions, and not related in time to eating. Within the past two weeks he had vomited every day. During the past week his stools had been black and associated with marked constipation. The vomitus was sometimes almost all liquid, brown or greenish in color, but not "coffee-ground" in appearance. The patient was referred to one of us (A. V. P.) with a diagnosis of bleeding and perforating gastric ulcer, as substantiated by x-ray studies.

Physical examination was essentially negative except for some tenderness and slight rigidity in the epigastrium.

*Laboratory Tests.*—R. B. C., 3,870,000; hemoglobin, 64.9; total protein plasma, 5.85; urine, negative; fractional meal analysis, lowest free HCl, 31 degrees, highest 75 degrees; Kalin test, negative; stool examination showed occult blood, 1 plus.

*X-ray Examination.*—The following report was given on the x-ray examination made upon admittance at Mercy Hospital:

"The fluoroscopic examination made with the radiopaque medium revealed the emulsion entering the esophagus freely and dilated it normally. There was no evidence of lagging at the cardia. The stomach filled readily with the greater curvature reaching the level of the crest of the ilium in the median line. Peristaltic function was hyperactive with the waves not closing off accurately to the tip due to effects on the lesser and greater curvature of the pylorus at the antrum. The first portion of the duodenum showed a diverticulum in the inferior surface, and several defects on the superior surface. The second portion of the duodenum showed the barium passing through it, without any evidence of peristalsis, in a thin stream. The proximal end of the third portion of the duodenum was markedly dilated, and antiperistalsis was very evident. Patient complained of tenderness upon palpation over the defects.

"The five-hour roentgenogram showed some retention of the barium in the diverticulum, and the remainder of the barium distributed throughout the colon."

*Preoperative Diagnosis.*—Bleeding and chronic perforation ulcer; chronic duodenal obstruction due to an embryonal band fixing the first loop of jejunum; possible gastroduodenal fistula.

*Operative Findings.*—There was a stellate scar on the anterior surface of the pylorus. The pyloric end of the stomach and the first part of the duodenum were firmly adherent together, and apparently a fistulous tract communicated between them. The head of the pancreas was slightly enlarged. The first loop of jejunum was found adherent to the transverse mesocolon, and its direction was to the right of the body (Fig. 8).

*Procedure.*—The embryonal band was excised, and the first loop of jejunum restored to its normal position. A partial gastrectomy was performed.

#### *Pathologic Report.*—

"Specimen consists of a pyloric segment of the stomach measuring 14 cm. in length. Peritoneum covering what is apparently the anterior surface of the stomach is smooth and reddish gray in color. That covering which is apparently the posterior aspect seems roughened by torn fibrous adhesions. The mucosa is swollen, reddish

*Physical Examination.*—The head and neck were essentially negative. The abdomen showed hypogastric tenderness and abdominal distention, and was thin, wrinkled, and inelastic. There was slight tenderness in the epigastrium. The liver edge was palpable. The patient was poorly nourished, emaciated, apathetic, tired, lying quietly in bed and appearing rather acutely ill.

*X-ray Examination.*—“Fluoroscopic examination of the stomach, by means of barium meal, revealed the emulsion passing through the esophagus freely. The stomach filled readily with the greater curvature reaching below the crest of the ilium, with the patient in the vertical position. The peristaltic function was hyperactive. The pylorus closed off accurately to the tip of the antrum. The first and second portions of the duodenum revealed a marked dilatation, and at no time did any barium pass beyond the second portion of the duodenum due to a stenosis or constriction. The roentgenograms taken immediately after confirm the fluoroscopic findings [Fig. 14]. Five-hour roentgram reveals about 40 per cent of the barium in the stomach [Fig. 15], with about 30 per cent of it in the first and second portion of the duodenum which is markedly dilated.”



FIG 14 —Case 5. Hodgkin's disease. Immediate plate showing an enlarged duodenum.

The patient died on Sept. 29, 1939, eleven days after admission. Autopsy was performed by Dr. J. P. Sheehan. The following is a brief résumé of his report: Marked dilatation of the stomach, first, second, and third portions of the duodenum. Pylorus fully 6 cm. in diameter, and the duodenum 6 to 8 cm. The lymph nodes around the origins of the superior mesenteric artery and celiac axis were markedly enlarged, particularly those to the right of the aorta. The posterior aspect (dorsal)



progressively more pronounced, copious in amount, and finally continuous. Medical treatment and cholecystectomy failed to relieve these symptoms. These facts coupled with x-ray findings indubitably indicated a duodenal obstruction. A tumor was suspected as being the cause of the obstruction because of the sudden onset of the symptoms, and the absence of any previous history of "gastric distress." The patient was in a precarious condition, and a duodenojejunostomy was performed because it was felt that this was the only procedure which offered any hope of relief.



Fig. 13.—Case 4. Carcinoma of the terminal duodenum. Five-hour plate shows retention in the duodenum.

CASE 5.—Mrs. C. A., aged 60 years.\* On admission to Mercy Hospital the patient complained of intermittent vomiting associated with pain in the epigastrium, loss of weight (she had weighed 127 pounds about ten months before and at present weighed 79 pounds), constipation, nocturnal frequency, and occasional edema.

The patient stated that she had been well until about one and one-half years before admission when she began to have vomiting attacks associated with pain in the epigastrium. During the past year she had been under medical treatment; nevertheless, the symptoms had become more severe. She had a sick feeling after eating rich foods. During the past few months the condition had been getting much worse, and the patient had lost considerable weight. At present she vomited after each meal, and the vomitus was deeply bile stained. Stools were clay colored.

\*This case is reported through the courtesy of Dr. George D. Griffin.

tinged fluid with no free hydrochloric acid present. A barium meal showed the stomach filled normally; it was located to the left extending down to the pelvis; the duodenum was distended and filled with barium in its first, second, and third positions up to the lumbar spine (Fig. 16). A four-hour plate revealed 60 per cent gastric residue with some retention in the duodenum; a six-hour plate revealed 40 per cent residue; a twenty-four-hour plate revealed the stomach empty.



Fig. 16.—Case 6. Aneurysm of the abdominal aorta. Immediate plate showing the duodenum filled with barium up to the spine. Note the displacement of the stomach caused by the pressure of the aneurysm.

A diagnosis was made of a subacute duodenal obstruction due to a pancreatic cyst or an abdominal aneurysm. The patient was placed in bed with elevation of the foot of the bed, and given six feedings of a bland diet daily. Surgery was deemed inadvisable due to patient's age. Vomiting stopped, and the patient felt improved. Small frequent feedings and bed rest were continued, and the patient gained 10 pounds (95 to 105 pounds) in a period of three months. He was kept on the infirmary service where he could rest in bed the greater part of the day. Vomiting did not recur.

On Sept. 28, 1939, patient suddenly collapsed and died. The following is a brief résumé of autopsy findings: The abdominal cavity contained large amounts of blood, in the retroperitoneal space and in the mesentery. There were 2,000 c.c. of free blood present in the cavity. The aorta was perforated (3 cm. in diameter) in the posterior wall about 8 cm. above the bifurcation. The aorta from the superior mesenteric origin to its bifurcation was markedly dilated, and formed a sac of about the size of a baby's head. The wall was very thin, and thrombotic masses were present in the sac. The stomach and duodenum were not dilated.

of the root of the mesentery was firmly adherent to the anterior wall of the third portion of the duodenum. Proximal to this area of adhesions the duodenum was markedly dilated; distally the small intestine was partly collapsed.

*Microscopic Diagnosis.*—Hodgkin's disease, involving the upper abdominal nodes along the aorta, and in the root of the mesentery of the small bowel. Invasion of the wall of the third portion of duodenum by tumor from adjacent mesenteric nodes with formation of large ulcer in the third portion of the duodenum.



FIG. 15—Case 5 Hodgkin's disease. Five-hour plate shows about 30 per cent of the barium in the duodenum. Arrow indicates the sharply demarcated duodenum.

CASE 6.—Mr. J. S., aged 81 years. Duodenal obstruction due to huge aneurysm of abdominal aorta. The patient was committed to the Elgin State Hospital in 1935 and classified as psychosis with cerebral arteriosclerosis. During January, 1939, he complained of attacks of upper abdominal pain and vomiting of bile stained fluid. Vomiting seemed to occur more frequently after meals and was followed by relief of epigastric fullness and distress. Examination revealed a thin male 81 years of age, not appearing acutely ill. Essential findings were localized to the abdomen. There was a grapefruit sized semifirm mass in the epigastrium which extended to the right costal margin, but did not appear to be attached to the liver. Pulsation was present, but did not appear to be expansile in type. Laboratory tests revealed normal blood count, negative urinalysis and blood Wassermann, with an elevation of the N.P.N. to 47.1 mg. and creatinine to 1.90 mg. (elevation possibly due to repeated vomiting). The Ewald test meal revealed 400 c.c. of bile.

tinged fluid with no free hydrochloric acid present. A barium meal showed the stomach filled normally; it was located to the left extending down to the pelvis; the duodenum was distended and filled with barium in its first, second, and third positions up to the lumbar spine (Fig. 16). A four hour plate revealed 60 per cent gastric residue with some retention in the duodenum; a six hour plate revealed 40 per cent residue; a twenty-four hour plate revealed the stomach empty.



Fig. 16—Case 6. Aneurysm of the abdominal aorta. Immediate plate showing the duodenum filled with barium up to the spine. Note the displacement of the stomach caused by the pressure of the aneurysm.

A diagnosis was made of a subacute duodenal obstruction due to a pancreatic cyst or an abdominal aneurysm. The patient was placed in bed with elevation of the foot of the bed, and given six feedings of a bland diet daily. Surgery was deemed inadvisable due to patient's age. Vomiting stopped, and the patient felt improved. Small frequent feedings and bed rest were continued, and the patient gained 10 pounds (95 to 105 pounds) in a period of three months. He was kept on the infirmary service where he could rest in bed the greater part of the day. Vomiting did not recur.

On Sept 28, 1939, patient suddenly collapsed and died. The following is a brief résumé of autopsy findings: The abdominal cavity contained large amounts of blood, in the retroperitoneal space and in the mesentery. There were 2,000 c.c. of free blood present in the cavity. The aorta was perforated (3 cm. in diameter) in the posterior wall about 8 cm. above the bifurcation. The aorta from the superior mesenteric origin to its bifurcation was markedly dilated, and formed a sac of about the size of a baby's head. The wall was very thin, and thrombotic masses were present in the sac. The stomach and duodenum were not dilated.

## SUMMARY

1. The terminology used to describe the various types of duodenal obstructions is in a chaotic state. We suggest that the term duodenal obstruction be applied universally regardless of the etiological factor.

2. Duodenal obstruction has been classified according to the etiological factors. This classification should be of material aid toward a more complete understanding of the subject. The etiological factors are divided into two general groups; (a) those which are basically of congenital origin, and (b) those which are acquired.

3. The pathologic anatomy of the duodenum has been thoroughly discussed and the pathogenesis of arteriomesenteric obstruction, gastromesenteric ileus, and other types of duodenal obstruction is given.

4. The diagnosis of duodenal obstruction may be easily arrived at in some cases, while in others it may not be so obvious. No single symptom, or combination of symptoms and physical findings, is pathognomonic. A thorough knowledge and familiarity of the subject and the utilization of this knowledge in the differential diagnosis of all obscure upper abdominal diseases are essential to arrive at a correct diagnosis of duodenal obstruction. Careful roentgen studies will confirm the diagnosis in practically every case.

5. Both medical and surgical treatments are discussed. We stress the fact that each case demands individual consideration. Medical treatment for the viscerotonic type is given in detail. Criteria for surgical indications are given, and the choice of operation is also discussed.

6. Six cases are reported: (1) typical arteriomesenteric obstruction, (2) megaduodenum due to adherent transverse colon into the pelvis, (3) embryonal band attaching about 3 inches of the jejunum to the transverse mesocolon associated with perforation and bleeding ulcers, (4) carcinoma of the terminal duodenum, (5) duodenal obstruction by extension of glands from Hodgkin's disease, and (6) duodenal compression due to pressure from an aneurysm of the abdominal aorta.

## REFERENCES

1. Bagen, J. A., and Walters, W.: Primary Duodenal Obstruction With Toxemia, Duodenojejunoscopy, Report of a Case, Proc. Staff Meet. Mayo Clin. 8: 321-324, 1933.
2. Bloodgood, J. C.: Acute Dilatation of the Stomach Gastro-Mesenteric Ileus, Ann. Surg. 46: 736, 1907.
3. Bloodgood, J. C.: Dilatation of the Duodenum, J. A. M. A. 59: 117, 1912.
4. Buchanan, E. P.: Congenital Duodenal Obstruction From Anomalous Mesenteric Vessels, Am. J. Surg. 30: 499-501, 1935.
5. Dragstedt, L. R., Montgomery, M. L., Ellis, J. C., and Matthews, W. B.: The Pathogenesis of Acute Dilatation of the Stomach, Surg., Gynec. & Obst. 52: 1075-1086, 1931.
6. Halpert, B.: Zur Frage . . . mesenterialen Duodenalverschlusses Nebst Bemerkungen Ueber Albinurie, Virchow's Arch. 244: 439-466, 1923.
7. Halpert, B.: The Arteriomesenteric Occlusion of the Duodenum: An Anatomical Study, Bull. Johns Hopkins Hosp. 38: 409-422, 1926.

8. Jewett, C. H.: Chronic Duodenal Ileus: With Especial Reference to Treatment, *J. A. M. A.* 91: 91-95, 1928.
9. Jordan, A. C.: Duodenal Obstruction as Shown by Radiography, *Brit. M. J.* 1: 1172-1174, 1911.
10. Kellogg, E. L.: Diagnosis and Treatment of Chronic Duodenal Obstruction, *Surg., Gynec., & Obst.* 28: 174-182, 1918.
11. Kellogg, E. L.: Abnormalities in the Shape and Position of the Duodenum, *Am. J. Surg.* 12: 462-465, 1931; 13: 227-234, 1931.
12. Kellogg, E. L.: Intussusception of the Duodenum, *M. J. & Rec.* 134: 440-442, 1931.
13. Kellogg, E. L., and Kellogg, W. A.: The Duodenum, A Surgical Monogram, 1933, Paul B. Hoeber, Inc.
14. Kellogg, E. L., and Collins, J. T.: Congenital Duodenal Obstruction, *Am. J. Surg.* 30: 369-371, 1935.
15. Kellogg, E. L., and Kellogg, W. A.: Chronic Duodenal Ileus, *Radiology* 9: 23-38, 1927.
16. Kellogg, E. L., and Kellogg, W. A.: Chronic Duodenal Obstruction With Duodenojejunostomy as a Method of Treatment. Report of 41 Operations, *Ann. Surg.* 73: 578-608, 1921.
17. Lane, Sir A.: Clinical Lecture on Chronic Intestinal Stasis, *M. Press* 96: 522-525, 1913.
18. Lane, W. A.: An Address on Chronic Intestinal Stasis, *Brit. M. J.* 1: 1408-1411, 1909.
19. Lane, W. A.: The First and Last Kink in Chronic Intestinal Stasis, *Lancet* 2: 1540-1541, 1911.
20. Lichty, J. A.: The Symptomatology and Diagnosis of Chronic Duodenal Ileus, *Clifton M. Bull.* 10: 48-52, 1924.
21. Mayo, W. J.: The Relation of the Mesocolic Band to Gastroenterostomy, *Ann. Surg.* 47: 1-3, 1908.
22. Schnitzler: *Wien. Klin. Rundschau.* 9: 579, 1895.
23. Shattuck, H. F., and Imboden. H. M.: Chronic Intermittent Duodenal Obstruction, *J. A. M. A.* 98: 943-947, 1932.
24. Vanderhoof, D.: Chronic Occlusion of the Duodenum in Visceroptosis: Based on a Study of 28 Cases, *Virginia M. Monthly* 50: 591-594, 1923.
25. Waugh, G. E.: The Morbid Consequences of a Mobile Ascending Colon, With a Record of 180 Operations, *Brit. J. Surg.* 7: 343, 1920.
26. Wolfer, J. A.: Chronic Duodenal Obstruction, *Radiology* 9: 39-42, 1927.

## OBSTRUCTION OF THE STOMACH DUE TO CONGENITAL DOUBLE SEPTUM WITH CYST FORMATION

ARTHUR R. METZ, M.D., RAYMOND HOUSEHOLDER, M.D., AND  
JAMES F. DEPREE, M.D., CHICAGO, ILL.

COMPLETE obstruction of the stomach due to a congenital double septum with mucosal cyst formation is a rare anomaly, which is the reason for reporting such a case. A careful search of the medical literature in an effort to obtain more information on the subject revealed one case of a cyst of the stomach causing obstruction at birth. In that case there was a lumen through the stomach which was compressed by the distended cyst. A second case has recently been reported of a congenital prepyloric membranous obstruction in a premature infant.

It has been estimated that congenital obstruction of the upper intestinal tract occurs once in 20,000 infants. We have been able to find only one case reported in the literature of complete obstruction of the stomach by a septum or cyst formation in the newborn infant that survived after operation.

Touroff and Sussman<sup>1</sup> recently reported a case of congenital prepyloric membranous obstruction in a premature infant which was operated upon Sept. 16, 1938, on the fifth day of life, and the patient lived. They describe a true mucous membrane septum obstructing the stomach just proximal to the pylorus which was incised radially in several directions, after which the incision in the duodenum and stomach was closed by doing a Heineke-Mikulicz pyloroplasty. Touroff and Sussman made a survey of literature and were unable to find a report of a similar mucous membrane septum obstructing the stomach.

Our attention was drawn to this subject by the following case which we wish to report:

On Aug. 5, 1937, a Jewish male infant, weighing eight pounds and three ounces, was born at the Washington Boulevard Hospital, Chicago. It was the first child of healthy parents and appeared to be perfectly normal. Six hours after delivery the child vomited chocolate-colored mucus and continued to regurgitate mucus and milk every two to four hours for the following three days. On the third day a small movable mass about 5 cm. in diameter was palpated just above the umbilicus. A diagnosis of an obstruction of the stomach or intestine was made and an immediate operation was advised.

*Operation.*—Under local anesthesia supplemented by chloroform the abdomen was opened through a right upper rectus incision. The mass which had been palpated was found to be firm and cystlike and located in the distal third of the stomach extending up to the pylorus. No other evidence of pathology could be seen or palpated in the abdomen.

A longitudinal incision was made into the gastric mass and about 15 c.c. of slightly turbid mucous fluid escaped. By enlarging the incision to about 4 cm. in length it was noted that the cyst occupied the entire lumen of the stomach, and that the lining membrane had the gross appearance of normal gastric mucosa.

A second incision made in the anterior wall of the stomach proximal to the cyst showed the lumen of the stomach to be completely occluded by the cyst. An eight-inch forceps was then forced from the proximal stomach side of the cyst through the septum into the cyst proper and this opening was enlarged by three radial incisions until it was 3 cm. in diameter.

An incision was then made into the duodenum 3 cm. distal to the pylorus, large enough to insert an eight inch forceps. A similar obstruction was found just proximal to the pylorus, and through this the forceps was pushed into the cyst. This opening into the distal septum was enlarged by three radial incisions making an opening about 2 cm. in diameter.

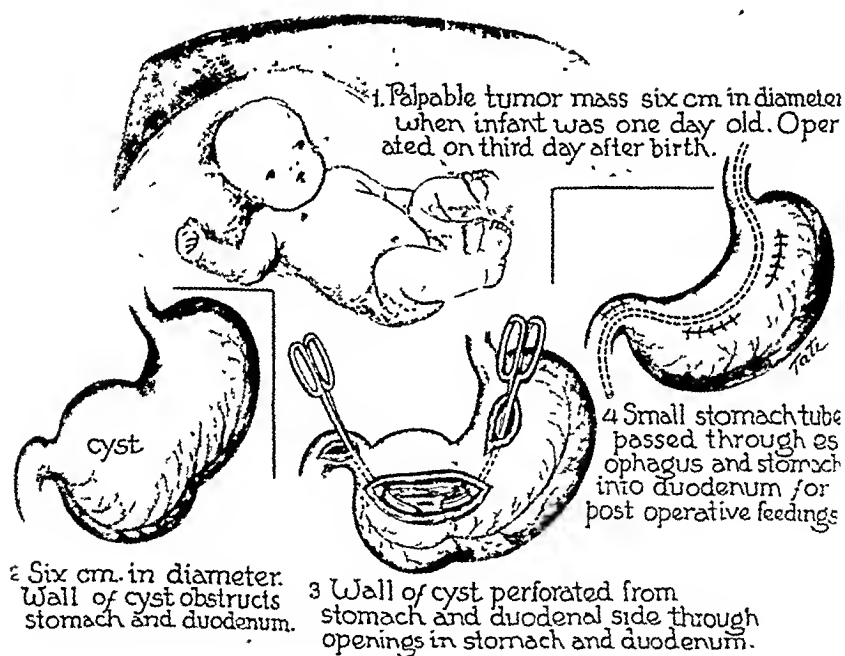


Fig 1

A nasal tube which had been passed into the stomach was now advanced through the openings in the two walls of the cyst into the duodenum.

The incisions in the stomach and duodenum were closed with two rows of sutures and the abdominal incision closed without drainage.

The infant was fed through the nasal tube for two days, supplemented by subcutaneous fluids. On the third postoperative day the child was put to the breast. The one pound and three ounces which the infant had lost during the first three days of life before operation were regained in the next fourteen days. Two weeks after operation the child was so well that he successfully sustained a ritualistic circumcision.

In December, 1940, the boy, 3 years and 2 months old, three feet six inches tall, and weighing thirty eight pounds, was in excellent health. A roentgenologic



examination of his stomach with a barium meal showed the stomach to be normal in size and shape with no evidence of filling defect. The pylorus was patent and appeared to be functioning normally.

*Pathologic Report.*—The gross appearance of the lining of the cyst was entirely similar to that of the lining of the stomach. Microscopic examination of sections taken from the septum between the cyst and the stomach showed normal gastric glands on both sides with smooth muscle fibers in between.

From examination of the stomach at the time of operation it was impossible to determine the origin of the cyst. Evidently two septa developed in the stomach with the creation of a closed cavity in between. With the beginning of gastric function the gastric juice in the closed space formed a cyst.

#### SUMMARY

A case is presented of complete congenital obstruction of the stomach by a mucosal cyst in a newborn infant which was successfully operated upon the third day of life.

The cyst, which was gastric in origin, probably resulted from the formation of two septa in the stomach.

Microscopic examination of the lining membrane showed the presence of gastric glands.

The operative technique as described consisted of re-establishing the lumen through the stomach by perforating the walls of the cyst.

A review of the medical literature shows this condition to be very rare, and this case is reported in order to add to our present small knowledge of this subject.

#### REFERENCE

1. Touroff, Arthur S., and Sussman, Ralph M.: Congenital Prepyloric Membranous Obstruction in a Premature Infant, *SURGERY* 8: 739, 1940.

## SPINAL EXTRADURAL CYSTS

FRANK H. MAYFIELD, M.D., CINCINNATI, OHIO, AND

EVERETT G. GRANTHAM, M.D., LOUISVILLE, KY.

(From Department of Surgery, University of Louisville School of Medicine,  
Louisville, Ky.)

THE PRIMARY purpose of this report is to record the case records of two additional spinal extradural cysts. This addition brings the total number of proved cases of the malady to 16. The secondary purpose of the report is to re-emphasize the thesis that the lesion is more common than reports thus far would indicate and that the lesion can simulate the clinical picture of degenerative lesions of the spinal cord, especially multiple sclerosis.

In 1934, Elsberg, Dyke, and Brewer<sup>4</sup> reported 4 cases of spinal extradural cyst, 3 of which had occurred in their series of 250 tumors of the spinal cord. The fourth case had been operated upon by Dr. A. S. Taylor. From their study, Elsberg, Dyke, and Brewer presented as the characteristic syndrome the following: "The individual is an adolescent with the history and symptoms of progressive spastic paraplegia. Pain is absent or is not a prominent symptom. The objective disturbance of sensibility is slight and the upper level is in the midthoracic region, usually in the sixth or seventh thoracic dermatome." They also noted narrowing and atrophy of the pedicles of the vertebrae in the middorsal region with widening of the interpediculate space. They theorized that this variety of spinal extradural cyst was due to a congenital diverticulum of the dura or a herniation of the arachnoid through a congenital defect of the dura.

One year later Lehman<sup>7</sup> reported 2 cases of spinal extradural cyst. His cases showed the clinical features which Elsberg, Dyke, and Brewer had described as characteristic of the syndrome, but, in addition, he called attention to x-ray changes in the body of the vertebra, an epiphysitis, which he considered an additional reason for suspecting the presence of an extradural cyst. He also emphasized the great variability in the clinical findings which these lesions produced as compared with other expanding lesions of the spinal canal. He concluded that the cysts were a herniation of the arachnoid through a congenital defect of the dura since in 1 of his cases there was a neck which was patent connecting the cyst with the dura. Elsberg, Dyke, and Brewer had suggested that "if the hypothesis that the cyst is due to herniation of the arachnoid through a congenital defect of the dura is correct, cases might be encountered in which the neck of the sac had not been obliterated."

Cloward and Buey<sup>2, 3</sup> reported 2 cases and made an extensive study of the x-ray changes presented by ten of the spinal extradural cysts. They called attention to the fact that the kyphosis seen with spinal extradural cysts is identical with that described as kyphosis dorsalis juvenilis. They concluded that these bony changes are due to compression and occlusion by the cyst of the venous channels draining the vertebral bodies. They also believed that the cyst is a diverticulum of both dura and arachnoid. The case reported by Cloward was unusual in that the cyst occurred in an adult, and its location was in the lumbar region.

Mixter's<sup>9</sup> case was unusual in that the cyst was multilocular.

Peet and Kahn<sup>10</sup> reported a case of spinal extradural cyst in which the principal symptoms were vascular, not unlike those occurring in Raynaud's disease. In none of the other reported cases were vascular phenomena observed.

Meredith<sup>8</sup> reported a case of spinal extradural cyst occurring in the cervical region. This is the only case recorded in the cervical region. He believed the cyst resulted from a trauma with a puncture of the dura by a sliver of bone.

Recently Kelly,<sup>5</sup> Turnbull,<sup>14</sup> and Robertson and Graham<sup>11</sup> have each added an additional case to the literature.\*

#### CASE REPORTS

**CASE 1.**—M. S., white male, aged 16 years, was admitted to Norton Memorial Infirmary, Louisville, Ky., on Feb. 28, 1937, because of weakness of the legs.

The past and family histories were irrelevant.

The present illness started three years before when the patient fell and wrenched his back badly. He immediately had severe shooting pains down his right leg. Soon both legs became numb and weak, and he was unable to walk. He was bedridden for several weeks at the time with marked loss of sensation from the inguinal region downward. He improved gradually, and, after approximately three months, was able to resume his normal activities.

One year later while driving a truck he applied the brakes suddenly and felt a snapping sensation in his back followed by violent pain which shot down the right leg and, to a less degree, down the left leg. He was able to continue driving for a short while, but when he got out of the truck both legs collapsed under him. Numbness and tingling were present in both legs.

Some improvement of strength in his legs occurred, but he had been unable to walk without crutches for approximately eighteen months. There had never been incontinence of urine or feces. He had suffered no pain for over a year. The weakness of both legs had gradually progressed for the four weeks preceding admission.

*Physical examination* showed a slightly obese, white male, weighing 220 pounds and measuring 6 feet in height. Both legs were moderately spastic with weakness

\*The cases of Schlesinger<sup>12</sup> and Krauss,<sup>6</sup> sometimes included in the reports of spinal extradural cysts, are not considered acceptable as proved cases of the syndrome here discussed.

Cloward and Buey<sup>3</sup> discovered a report by Blum<sup>1</sup> of a case which was probably a spinal extradural cyst.

Teachenor<sup>13</sup> reported a spinal extradural cyst at the Harvey Cushing Society in Philadelphia in 1937. Certain details of this case were included by Cloward and Buey<sup>3</sup> through a personal communication, but a complete report has never been published.

more pronounced in the right leg. Knee and ankle jerks were markedly exaggerated bilaterally. There was a sustained patellar and ankle clonus and a positive Babinski, Oppenheim and Gordon bilaterally. The upper extremities were normal.

Below the iliac crest there was marked loss of all forms of sensation. Above this point to the level of the eighth dorsal segment the sensory loss was less pronounced. Above the eighth dorsal segment sensation was normal.

Spinal puncture yielded clear, colorless fluid. There was a complete subarachnoid block to Queckenstedt test. X-rays of the dorsal region showed a rather marked kyphosis in the lower dorsal region. The following note was made on the x-ray report: "The anterior margins of the dorsal vertebrae are slightly irregular undoubtedly indicating that the patient has had an epiphysitis early in life and that the picture now present is what is known as juvenile kyphosis dorsalis. The pedicles of the dorsal vertebrae seem to be normal."

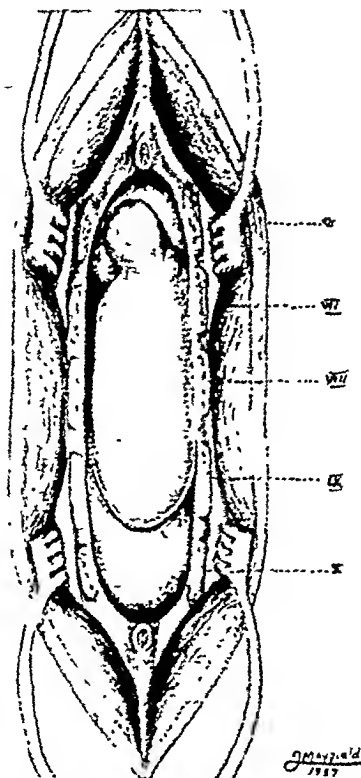


Fig. 1—Schematic drawing showing the position of the cyst overlying the dural sac. Pressure on the cystic cavity caused it to empty, and compression of the jugular veins immediately distended the cyst.

Lipiodol examination showed an incomplete block at the lower margin of the tenth dorsal vertebra. The lipiodol gradually passed around this obstruction to re-form underneath the ninth dorsal vertebra.

Operation.—On March 8, 1937, a laminectomy of the sixth, seventh, eighth, ninth, and tenth dorsal vertebrae was performed (F. H. M.). When the laminae were removed, a tense cystic mass was exposed which was easily freed from the underlying dura (Fig. 1). As the cyst was being manipulated it became softer and finally collapsed. All of the fluid within the cyst had escaped through the patent

pedicle into the subarachnoid space. When the patient coughed or when the jugular veins were compressed the cyst would refill. This refilling and emptying process was demonstrated several times during the operative procedure. A silver clip was applied to the pedicle and the entire cyst lifted from the wound. The pedicle was attached to the dura near the exit of the ninth spinal nerve on the right side.

*Pathologic examination* showed a cystic mass measuring 16 by 20 by 60 mm. The microscopic study showed the wall to be composed of dense, white, fibrous tissue similar to that seen in normal dura. The inner portion of the wall was of more loosely constructed connective tissue. A few flattened cells similar in appearance to the arachnoid were found on the inner wall.

*Postoperative course* was uneventful. At the time of discharge two weeks later, the patient could walk without support, and the sensation was normal. Tendon reflexes were still hyperactive, but there were no pathologic reflexes. He was given a back brace and instructed to wear it for six months.

At our request, the patient returned for examination on Oct. 1, 1940. He stated that he had been employed at heavy work since he discontinued the use of the back brace and had recently volunteered for military service.

Examination at that time revealed a moderately exaggerated dorsal kyphosis and completely normal neurological findings.

*Comment.*—This case represents two unusual features. The onset of symptoms occurred immediately following trauma. After a short period of definite spinal cord compression, the patient apparently had a complete recovery. A year later, following a second minor trauma, the signs of spinal cord compression recurred. In no other case of spinal extradural cyst has a history of trauma been so closely associated with the onset of symptoms. At operation the finding of a pedicle, which was patent, connecting the cyst and the subarachnoid space afforded proof to the theory that the cysts are arachnoidal herniations that may empty and fill intermittently. At the time of operation the cyst was filled completely and during manipulation emptied into the subarachnoid space. The remission, as related in the history, was probably due to a similar emptying of the cyst.

CASE 2.—C. B., negro male, aged 26 years, was admitted to the Louisville City Hospital on April 1, 1940, because of weakness of the legs. The only significant feature in the past history was that one year previous to the onset of his symptoms he fell from a barn, fracturing his left arm. He could not remember sustaining other injuries at the time.

Twelve years ago the patient noted that the left foot "went to sleep" easily. Soon after the onset of this tingling sensation the left foot became weak, and he was forced to lift it high when walking. Numbness developed in the left leg and gradually spread upward. Soon both legs were involved. By the end of a year he was unable to walk. Both legs felt numb and dead.

It was fourteen months before any improvement was noted. Then the sensation in his legs gradually returned, and he was soon able to get around with the use of a cane. Following his first episode he had weakness and numbness of the legs followed by four definite remissions. He was unable to give accurately the dates of these remissions. With each episode of paralysis the recovery was less complete. For the preceding three years the paralysis had slowly progressed without any semblance of a remission. During the last year he had been bedfast with very

little voluntary movement possible in either leg. His whole body below the umbilicus felt numb and dead. For three months he had noted difficulty in voiding and was markedly constipated. For two or three months he had noted numbness of both hands, and his arms felt clumsy.

This patient was first examined in this clinic in October, 1939. The findings at this time were (1) spastic paraplegia with bilateral ankle clonus and bilateral Babinski responses, (2) diminution in all forms of sensation below the level of the umbilicus, (3) marked incoordination of the upper extremities with a bilaterally positive Hoffmann's sign. In view of the history of remissions and the findings in the upper extremities, a presumptive diagnosis of multiple sclerosis was made, but a complete investigation was advised, including x rays of the spine and spinal fluid examination. He did not return to this clinic, however, until March, 1940, and at this time the following positive findings were listed: (1) The voluntary control of both lower extremities was markedly reduced. (2) Mass reflexes were easily demonstrated in both lower extremities. (3) Tendon reflexes in both legs were hyperactive. (4) There was bilateral ankle clonus with bilateral Babinski signs. (5) Sensory examination showed a well-marked sensory loss from below the level of the tenth dorsal dermatome. All forms of sensation were equally involved. (6) The reflex activity of the upper extremities was hyperactive, but no pathologic reflexes were demonstrated. (7) X-rays of the dorsal spine showed marked atrophy of the pedicles of the sixth and seventh dorsal vertebrae with widening of the interpediculate spaces in these two vertebrae. The sixth, seventh, and eighth dorsal vertebrae were wedge shaped, characteristic of *kyphosis dorsalis juvenilis*. (8) Spinal puncture showed the fluid to be under 50 mm. of water pressure. There were no cells and no globulin, and the total protein was 270 mg. per cent.

*Operation.*—On April 8, 1940, laminectomy of the fifth, sixth, seventh, and eighth dorsal vertebrae was performed. The laminae were very thin and atrophic. A cystic tumor with a peculiar bluish discoloration was easily exposed. The cystic mass was separated from the underlying dural sac. In the process of removal the lower pole of the tumor was ruptured and clear fluid escaped; this had the appearance of cerebrospinal fluid. On the lower pole a fibrous pedunculated attachment to the dura was demonstrated just to the left of the midline. Repeated efforts were made to demonstrate the patency of the pedicle; this was never successful. Careful inspection showed the attachment to be to the spinal dura with no attachment to the dura of the seventh spinal root.

*Pathologic Report.*—(Dr. A. J. Miller.) Microscopy showed that the entire wall was made up of fibrous connective tissue which varied somewhat in thickness and density of the connective tissue. In some portions the collagenous fibrils were abundant and dense and hyaline, in other portions they were of the same character, but fewer and smaller. There was a moderate number of thin walled blood vessels supplying the tissue. A mesothelial like lining was present. Here and there throughout the wall were small foci of inflammatory reaction consisting of moderately dense deposits of lymphocytes arranged about blood vessels and some old hemosiderin deposit. (Fig 2)

*Postoperative Course.*—At the time of his discharge, on April 28, 1940, all motion of the lower extremities had returned, but he was still very weak. Complete sphincteric control had returned. The sensory line at the umbilicus was still present, but hypesthesia was less marked than on admission. Sustained patellar and ankle clonus was present, but no Babinski was obtained. Abdominal reflexes were absent.

The patient was last seen on Sept. 13, 1940, six months after his discharge from the hospital. The strength in his legs had improved to the extent that he had been doing farm work for the preceding two months. His legs were still handled with a little difficulty. The examination showed a mild hypesthesia below the iliac crest.

The abdominal reflexes were weakly active. The knee and ankle jerks were hyperactive. There was an unsustained ankle clonus but no Babinski.

*Comment.*—Points to be noted in this case are the history of trauma antedating the onset of symptoms, the four distinct remissions, and the marked, long-standing paraplegia with marked sensory loss which was followed by prompt, postoperative improvement. The pedicle attaching the cyst to the dural sac, while at the level of the emerging nerve root, was nearer the midline posteriorly than it was to the nerve root itself.

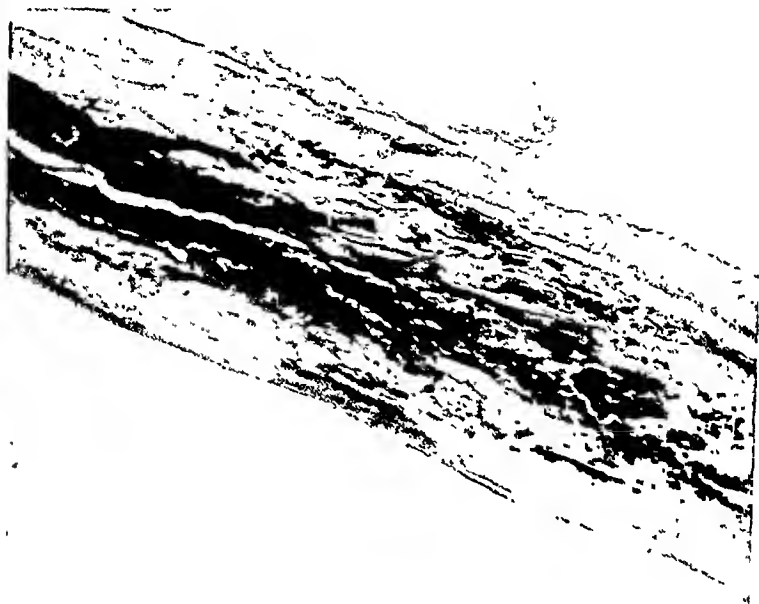


Fig. 2 —Photomicrograph of the cyst wall. Note the mesothelial-like lining, the lymphocytes about the blood vessels and old hemosiderin deposits

#### DISCUSSION

The first case demonstrated more accurately than any of the sixteen proved cases the communication of the cyst with the subarachnoid space. Such a finding was predicted by Elsberg, Dyke, and Brewer, who thought this would be confirmatory evidence of a herniation of the arachnoid through defect in the dura. Lehman<sup>7</sup> accepted this theory since his case indicated that the pedicle was patent.

It has been assumed by those who discussed the etiology that a congenital defect was present in the dura. The role of trauma in the production of the arachnoid herniation has received scant attention. Case 1 of this report indicates that trauma may be the exciting cause of symp-

toms. It may be assumed, therefore, that even though a congenital defect be present, trauma may produce herniation of the arachnoid through a congenital dural defect to form an extradural sac. All but one of the reported cases had onset of symptoms in adolescence, the majority of the patients being between 12 and 16 years of age.

Case 2 graphically illustrates the danger of dismissing these lesions as a degenerative disease. Other cases in the sixteen reported have been thought to be atypical multiple sclerosis at some time during the study. It is easy to understand why the case here presented was diagnosed as multiple sclerosis. The marked paraplegia with less marked loss in sensation and history of four remissions, plus the history of mild involvement of the upper extremities, might easily cause one to place the diagnosis in the category of atypical multiple sclerosis. On reviewing the cases reported it is found that remissions have not been an uncommon occurrence. Four have had spontaneous remissions and three others have been secondary to hyperextension. Lack of a history of pain, as is usual in these cases, plus a history of remissions, is very likely to mislead the examiner into making a diagnosis of nonneoplastic lesion. We feel that any patient with the onset of paraplegia in the adolescent period should have x-rays of his dorsal spine and a spinal puncture to eliminate the possibility of spinal extradural cyst.

#### REFERENCES

1. Blum, W.: Rückenmarksläsion bei Scheuermann'scher Krankheit (Kyphosis Dorsalis Adolescentium), *Schweiz. med. Wchnschr.* 66: 283, 1936.
2. Cloward, R. B.: Spinal Extradural Cysts, *Ann. Surg.* 105: 401, 1937.
3. Cloward, R. B., and Buey, P. C.: Spinal Extradural Cyst and Kyphosis Dorsalis Juvenilis, *Am. J. Roentgenol.* 38: 681, 1937.
4. Ellsberg, C. A., Dyke, C. G., and Brewer, L. D.: Symptoms and Diagnosis of Extradural Cysts, *Bull. Neurol. Inst. New York* 3: 395, 1934.
5. Kelly, T. S. B.: Non Parasitic Extradural Cyst of Spinal Canal, *Lancet* 2: 13, 1937.
6. Krauss, W. C.: A Case of Cyst Within the Spinal Canal, *Brain* 30: 535, 1907.
7. Lehman, E. P.: Spinal Extradural Cysts, *Am. J. Surg.* 28: 307, 1935.
8. Meredith, J. M.: Unusual Tumors and Tumor like Lesions of the Spinal Canal and Its Contents With Special Reference to Pitfalls in Diagnosis, *Virginia M. Monthly* 67: 675, 1940.
9. Mixer, W. J.: Spinal Column and Spinal Cord, in Lewis: *Practice of Surgery*, Hagerstown, Md., 1934, W. F. Prior Co., vol. 12, p. 127.
10. Peet, M. M., and Kahn, E. A.: Vasomotor Phenomena Allied to Raynaud's Syndrome, *Arch. Neurol. & Psychiat.* 35: 79, 1936.
11. Robertson, J. P., and Graham, C. P.: Spinal Extradural Cyst Associated With Kyphosis Dorsalis Juvenilis, *Ann. Surg.* 110: 285, 1939.
12. Schlesinger, H.: Beiträge zur Klinik der Rückenmarks und Wirbeltumoren, Jena, 1898, G. Fischer, p. 46.
13. Teichenor, P. R.: Case of Extradural Spinal Cyst, Associated With Spinal Epiphysitis (Unpublished), Read before the Harvey Cushing Society, Philadelphia, May 6, 1937.
14. Turnbull, F.: Spinal Extradural Cyst, *Canad. M. A. J.* 41: 250, 1939.



# A CASE OF SHOCK AND HYPERPYREXIA INDUCED BY INTRAVENOUS GLUCOSE INFUSION\*

## ITS TREATMENT

JOSEPH MEDOFF, M.D., AND S. BURTON, M.D., CHICAGO, ILL.

(From the Departments of Medicine, Gastro-Intestinal Research, and the Samuel Deutsch Serum Center, Michael Reese Hospital)

ALTHOUGH reactions following the intravenous injection of aqueous solutions of saline and glucose are not uncommon in hospital practice, the mild nature of these reactions seldom requires any therapy other than a cessation of the infusion. Fever, chills, vomiting, and gastrointestinal disturbances are the most frequent manifestations, with the fever usually subsiding spontaneously in four to six hours.<sup>1</sup> Such conditions, as well as hyperpyrexia accompanying heat and sunstroke, are not usually considered by the clinician to be of the nature of shock, and are not treated accordingly. Shock with hemoconcentration and other pathologic changes accompanying therapeutic hyperpyrexia has been described.<sup>2, 3</sup>

Recently we have observed a case in which hyperpyrexia (109° F. rectally) developed during an infusion of saline and glucose solutions, and was followed by severe shock. The therapeutic effect of some of the more commonly accepted drugs, and, of human serum, as agents in the treatment of this type of shock was studied by means of repeated laboratory determinations.<sup>3, 4</sup> At first drug therapy alone was employed and this period served as a control. This was followed by the institution of human serum therapy, in addition to the supportive measures already employed. The very favorable response to the latter form of therapy has prompted us to report the following case.

## CASE HISTORY

W. S., white, male, aged 67 years, entered Michael Reese Hospital on April 13, 1940, with a clinical picture of acute sepsis. No definite diagnosis could be established. Sulfonamide therapy seemed to be ineffective. Six weeks after admission, a thrombophlebitis of the left leg associated with edema of both lower extremities appeared and shortly afterward the fever subsided. He gained over 15 pounds in four weeks, and was discharged to a convalescent home in fairly good condition.

Two weeks later he again began to show evidence of sepsis with daily fever of 101 to 103° F.,† and was readmitted to the hospital. He appeared acutely ill and showed evidence of recent weight loss. The clinical impression supported by x-ray evidence was that of chronic fibroid apical tuberculosis (inactive) and a probable subsiding bronchopneumonia. Daily temperatures of 104° F. were recorded. Sulfapyridine, sulfathiazole, and blood transfusions did not improve his condition. He appeared more toxic and the pulmonary findings were more extensive.

\*Aided by the Rosetta Josephson Fund.

†All temperatures taken rectally.

Received for publication, Aug. 12, 1941.

On Sept. 23, 1940, the patient showed marked dehydration (temperature  $104^{\circ}$  F.; pulse, 130; respirations, 22), and therefore was given an intravenous infusion of 5 per cent glucose in normal saline solution. After about 100 c.c. of the solution had been administered, he suddenly developed a severe chill accompanied by cyanosis, tachycardia, and shallow rapid respiration (temperature,  $105^{\circ}$  F.; pulse, 130; respirations, 30). His blood pressure fell to 80/50. The infusion was discontinued, and 1 c.c. of 1:1,000 adrenalin hydrochloride was given intravenously. At 3:30 P.M. the patient was perspiring profusely, incontinent, and vomiting coffee-brown material (temperature,  $106^{\circ}$  F.; pulse, 134; respirations, 36). He was placed in a cold pack, but his temperature continued to rise to  $109^{\circ}$  F., the pulse was imperceptible, and the blood pressure was 50/30 at 4:00 P.M. At 4:30 P.M. his temperature was  $108^{\circ}$  F., pulse imperceptible, respiration rapid and shallow, blood pressure 40/?. The hematocrit reading of 62 indicated hemoconcentration. Oxygen and external heat were administered and the foot of the bed elevated. Repeated intramuscular and intravenous injections of 15 to 20 mg. of parendrine had no appreciable effect on blood pressure. After drug therapy and supportive measures had been employed without effect, 500 c.c. human serum was administered intravenously at 11:00 P.M. Blood pressure rose to 56/40 and temperature dropped to  $104^{\circ}$  F.; a hematocrit of 48 indicated that hemoconcentration had been overcome (11:30 P.M.). Another intravenous infusion of 500 c.c. of serum with 1,000 c.c. of glucose-saline solution was administered during the night.

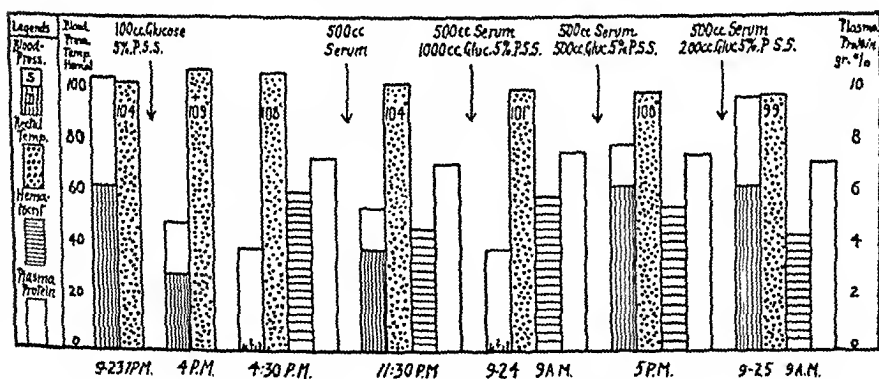


Fig. 1.—Graphic presentation of blood pressure, rectal temperature, hematocrit, and plasma proteins. The arrows indicate intravenous infusions. The first infusion of 100 c.c. 5 per cent glucose in physiologic salt solution was followed by hyperpyrexia and shock. Shock is indicated by low blood pressure (diastolic pressure could not be obtained), and high hematocrit (i.e. hemoconcentration). Supportive measures were of no avail, and are recorded in the body of the paper. Normal human serum with glucose in physiologic salt solution intravenously with supportive therapy were eventually followed by return of blood pressure and normal blood concentration. Specific gravity of plasma and total plasma proteins were determined by a modified Barbour and Hamilton falling-drop method.

On the following day, Sept. 24, 1940, at 9:00 A.M., blood pressure had again dropped to 40/?, temperature was  $101^{\circ}$  F., and hemoconcentration had reappeared (57 hematocrit and increased plasma protein level). The patient was stuporous and presented the picture of grave shock. At 4:30 to 5:00 P.M., an infusion of 500 c.c. of serum with 500 c.c. glucose-saline solution raised the blood pressure to 80/63, and diminished hemoconcentration appreciably (hematocrit, 54). During the night another intravenous infusion of 500 c.c. of serum and 200 c.c. of glucose-saline solution was administered.

On Sept. 25, 1940, at 9:00 A.M. (temperature,  $99^{\circ}$  F.; pulse, 118; respirations, 26), clinical evidence of shock was no longer present; blood pressure was 98/72 and later on rose to 104/70; hematocrit readings were normal (45); plasma pro-

# A CASE OF SHOCK AND HYPERPYREXIA INDUCED BY INTRAVENOUS GLUCOSE INFUSION\*

## ITS TREATMENT

JOSEPH MEDOFF, M.D., AND S. BURTON, M.D., CHICAGO, ILL.

(From the Departments of Medicine, Gastro-Intestinal Research, and the Samuel Deutsch Serum Center, Michael Reese Hospital)

ALTHOUGH reactions following the intravenous injection of aqueous solutions of saline and glucose are not uncommon in hospital practice, the mild nature of these reactions seldom requires any therapy other than a cessation of the infusion. Fever, chills, vomiting, and gastrointestinal disturbances are the most frequent manifestations, with the fever usually subsiding spontaneously in four to six hours.<sup>1</sup> Such conditions, as well as hyperpyrexia accompanying heat and sunstroke, are not usually considered by the clinician to be of the nature of shock, and are not treated accordingly. Shock with hemoconcentration and other pathologic changes accompanying therapeutic hyperpyrexia has been described.<sup>2, 3</sup>

Recently we have observed a case in which hyperpyrexia (109° F. rectally) developed during an infusion of saline and glucose solutions, and was followed by severe shock. The therapeutic effect of some of the more commonly accepted drugs, and, of human serum, as agents in the treatment of this type of shock was studied by means of repeated laboratory determinations.<sup>3, 4</sup> At first drug therapy alone was employed and this period served as a control. This was followed by the institution of human serum therapy, in addition to the supportive measures already employed. The very favorable response to the latter form of therapy has prompted us to report the following case.

## CASE HISTORY

W. S., white, male, aged 67 years, entered Michael Reese Hospital on April 13, 1940, with a clinical picture of acute sepsis. No definite diagnosis could be established. Sulfonamide therapy seemed to be ineffective. Six weeks after admission, a thrombophlebitis of the left leg associated with edema of both lower extremities appeared and shortly afterward the fever subsided. He gained over 15 pounds in four weeks, and was discharged to a convalescent home in fairly good condition.

Two weeks later he again began to show evidence of sepsis with daily fever of 101 to 103° F.,† and was readmitted to the hospital. He appeared acutely ill and showed evidence of recent weight loss. The clinical impression supported by x-ray evidence was that of chronic fibroid apical tuberculosis (inactive) and a probable subsiding bronchopneumonia. Daily temperatures of 104° F. were recorded. Sulfapyridine, sulfathiazole, and blood transfusions did not improve his condition. He appeared more toxic and the pulmonary findings were more extensive.

\*Aided by the Rosetta Josephson Fund.

†All temperatures taken rectally.

Received for publication, Aug. 12, 1941.

was without avail. The intravenous administration of normal human serum, in addition to the instituted therapy, brought the patient out of shock and restored normal circulation.

Hyperpyrexia is usually not recognized by clinicians as a possible cause of shock and therefore is not treated as such.

Our experience demonstrates that shock following infusion reactions may be very severe and that therapy has to follow the same principles as applied for other causes of shock, in which hemoconcentration, diminished blood volume, reduced volume flow, and low blood pressure are prominent features.

It is evident that restoration of normal circulating volume is imperative, and that only such fluids as serum or plasma, which will stay in the circulation, should be employed.

Adequate fluid therapy and clinical progress can best be controlled and maintained by blood studies.

We wish to acknowledge the advice and help of Dr. H. Necheles and Dr. S. O. Levinson.

#### REFERENCES

1. Co Tui, McCloskey, K. L., Schuft, A., and Yates, M. L.: A New Method of Preparing Infusion Fluids, *J. A. M. A.* 109: 4, 1937.
2. Kopp, I., and Solomon, H. C.: The Shock Syndrome in Therapeutic Hyperpyrexia, *Arch. Int. Med.* 60: 597, 1937.
3. Hartman and Major: Quoted by Moon, V. H.: The Occurrence and Clinical Significance of Hemoconcentration, *Ann. Int. Med.* 13: 451, 1939.
4. Scudder, J.: Blood Studies as a Guide to Therapy, Philadelphia, 1940, J. B. Lippincott Co.
5. Drew, C. R., Scudder, J., and Papps, J.: Controlled Capillary Phenomena, New York, 1938, Oxford Medical Publications.
6. Moon, V. H.: Shock and Related Capillary Phenomena, New York, 1938, Oxford Medical Publications.
7. Levinson, S. O., Neuwelt, F., and Necheles, H.: Human Serum as a Blood Substitute in the Treatment of Hemorrhage and Shock, *J. A. M. A.* 114: 455, 1940.
8. Levinson, S. O., Rubovits, F. E., Jr., and Necheles, H.: Human Serum Transfusions, *J. A. M. A.* 115: 1163, 1940.

teins were 7.3 Gm. per cent. The patient was now mentally alert and responded to all questions. Oxygen therapy was discontinued. The patient continued to be fairly well until on Sept. 29, 1940, when the pneumonic process extended. From then on the course was steadily downhill and he died on Oct. 3, 1940.

Necropsy findings were as follows: bilateral focal and confluent bronchopneumonia and chronic fibroidurative tuberculosis of the lung, involving the left apex; a moderate degree of bronchiectasis. A primary, ulcerative squamous-cell carcinoma of the lower portion of the esophagus with metastasis to the periesophageal and periaortic lymph nodes was an unsuspected finding. Although the entire wall of the esophagus was involved, the carcinoma was nonobstructive and it did not invade the mediastinum. The cause of the obscure fever was most likely due to the carcinoma and the lymph-node metastases. Death was due to inanition and a terminal bronchopneumonia.

#### DISCUSSION AND CONCLUSIONS

An infusion reaction in a debilitated patient resulted in an unusually severe hyperpyrexia, which was followed by profound shock. The manifestations of shock were an initial high hematocrit reading of 62 indicating hemoconcentration, two and one-half hours after the onset of the reaction; plasma proteins of 7.5 Gm. per cent; and a blood pressure of 40/?. The initial immediate treatment consisted solely of accepted supportive measures which did not appreciably affect the clinical status of the patient. Eight and one-half hours after the onset of hyperpyrexia and shock, normal human serum was given intravenously, and after 500 c.c. had been administered the hematocrit level had fallen to 48. The plasma proteins were 7.4 Gm. per cent, and the blood pressure was 56/40. Although nine and one-half hours later the blood pressure had fallen again, persistent intravenous therapy with serum supplemented by fluids (obtained from a different source than that which incited the reaction) resulted in steady improvement, until all evidence of shock had disappeared, the hematocrit being 45, the plasma proteins 7.3 Gm. per cent, and the blood pressure 98/72.

The treatment of shock in which hemoconcentration, diminished circulating blood volume, and reduced volume flow are prominent factors<sup>4</sup> has been shown both experimentally and clinically to be best controlled by the restoration of the fluid balance with fluids which will remain in the circulation for the greatest length of time. Normal serum and plasma best meet these requirements.<sup>7, 8</sup> The importance of controlling fluid therapy has been stressed.<sup>4, 5</sup> The recovery of this severely debilitated patient from shock accompanying hyperpyrexia indicates the value of human serum in the therapy of this type of shock and the distinct advantage of following the course and therapy with laboratory procedures.

#### SUMMARY

An intravenous infusion of saline-glucose solution was followed by extreme hyperpyrexia and severe shock. The usual supportive therapy

## PROCEDURE

Ambulatory patients were required to rest fifteen minutes prior to the experiment. The mouthpiece of the usual basal metabolism apparatus was inserted into the patient's mouth. In some cases, a tight-fitting surgical anesthetic mask was utilized instead of the mouthpiece. The rate and depth of respiration were recorded on a revolving drum in the same manner as a basal metabolism tracing. The blood pressure and pulse rate were recorded prior to the injection and at intervals of two minutes and ten minutes after the injection. The depth of respiration was measured in centimeters of needle excursion on the kymograph and the figures obtained transposed into cubic centimeters for volume of air inspired. The dosage of drugs administered was 0.48 Gm. aminophylline intravenously in one series of experiments, and 2 c.c. coramine intravenously in another series of experiments. Injections of normal saline solution were administered in a third control series.

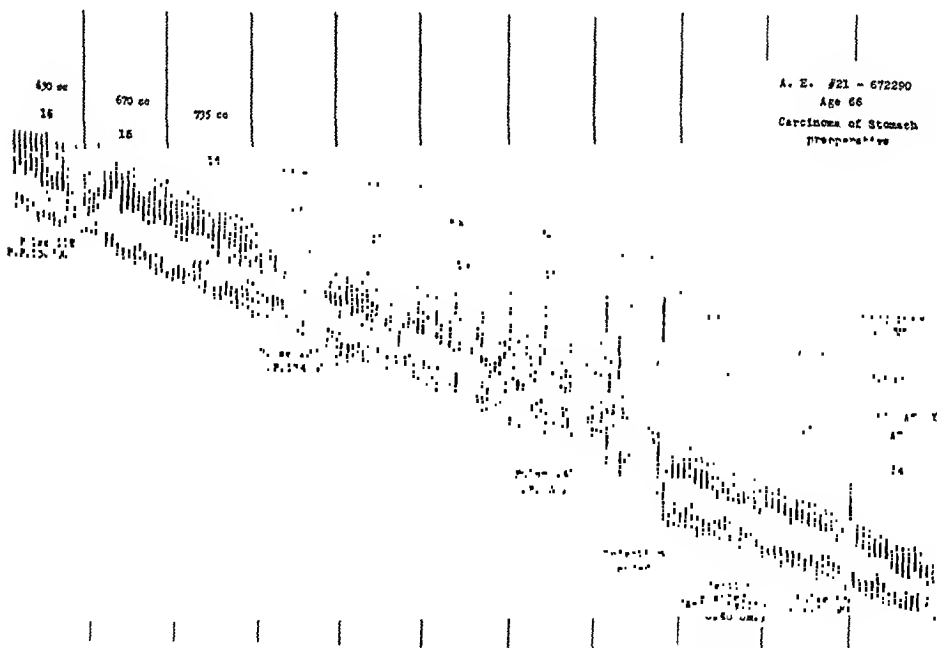


Fig. 1.—Respiratory tracing illustrating the effect of the intravenous administration of aminophylline.

## RESULTS

Twenty-two patients with no evidence of pulmonary involvement and three patients with postoperative atelectasis were given aminophylline. Of the twenty-two normal cases, there was a maximum immediate increase in rate averaging 26 per cent and an immediate increase of depth of respiration averaging 51 per cent. All cases showed an increase in the rate or depth or both occurring during the injections or

# THE EFFECT OF INTRAVENOUS THEOPHYLLINE WITH ETHYLENE DIAMINE (AMINOPHYLLINE)\* UPON THE RATE AND DEPTH OF RESPIRATION

## CLINICAL STUDY

LOUIS SPERLING, M.D., SYDNEY WEISMAN, M.D., AND  
RALPH PAPERMASTER, M.D., MINNEAPOLIS, MINN.

*(From the Department of Surgery, University of Minnesota)*

ASKANAZY reported in 1895 the use of caffeine and theobromine salts in the treatment of cardiac dyspnea. Since then, numerous investigators have studied the reaction of these drugs both in patients and in the experimental animal. Favorable results are reported by the majority of observers in the administration of these drugs for cardiac failure and cardiac pain.

Greene and co-workers have shown that the favorable influence of the intravenous administration of theophylline with ethylene diamine upon dyspnea is related to a fall of venous and intrathecal pressures. The arterial pressure does not seem to be affected. This would suggest a central action of the drug.

Smith and Sauls demonstrated an increase in skin temperature of the extremities for a period of three hours following intravenous administration of the drug.

Binger advocates its use in intravenous dextrose solution to increase diuresis and improve renal function. He states that there is less reaction to the intravenous administration of fluids when aminophylline is added to the solution.

Impressed by the deep and regular respiration induced by the intravenous administration to patients with Cheyne-Stokes respirations, it occurred to one of us (L. S.) that it might be worth while to administer the drug to patients during the immediate postoperative period to encourage increased diaphragmatic excursion and greater pulmonary ventilation as a prophylactic measure against postoperative atelectasis and subsequent pneumonia.

As far as we can determine, there have been no direct studies made on the effect of aminophylline on the rate and depth of respiration in man, nor of its use postoperatively to increase pulmonary aeration in an effort to prevent atelectasis.

This study was carried out upon patients in surgical wards of the University Hospital while they were awaiting operation and during their immediate postoperative convalescence.

\*Ampoules of aminophylline were supplied by G. D. Searle & Co  
Received for publication, July 28, 1941.

TABLE II  
CORAMINE SERIES

NAME	AGE	NORMAL RESPIRATORY RATE/MIN.	FASTEST RATE AFTER INJECTION	TIME TO FASTEST RATE IN MIN.	DURATION OF CHANGE IN RATE IN MIN.	NORMAL VOLUME OF RESPIRATION IN C.C.	VOLUME AFTER INJECTION IN C.C.	TIME TO GREATEST VOLUME IN MIN.	DURATION OF CHANGE IN RESPIRATORY VOLUME IN MIN.
H. 2 c.c.	23	21	22	0	0	610	630	0	0
A.B. 2 c.c.	33	19	17	0	0	545	755	0	1.0
M.C. 2 c.c.	48	18	19	0	0	735	795	1	0
G.P. 2 c.c.	19	25	23	0	0	480	610	1.5	10.0(?)
A.E. 2 c.c.	40	21	21	0	0	735	820	4	0.5
E.R. 3 c.c.	22	14	15	0	2	920	1,150	0	1.0
R. 1 c.c.		17	22	8	2	400	420	1	1.5
S. 1.5 c.c.	44	19	22	0.5	1	420	480	0	1.0



TABLE I  
AMINOPHYLLINE SERIES  
(0.48 GM. INTRAVENOUSLY)

NAME	AGE	NORMAL RESPIRATORY RATE/MIN.	FASTEST RATE AFTER INJECTION	TIME TO FASTEST RATE IN MIN.	DURATION OF CHANGE IN RATE IN MIN.	NORMAL VOLUME OF RESPIRATION IN C.C.	VOLUME AFTER INJECTION IN C.C.	TIME TO GREATEST VOLUME IN MIN.	DURATION OF CHANGE IN RESPIRATORY VOLUME IN MIN.
R.P.	60	21	29	0	11.0	840	1,210	0	11.0+
L.C.	35	30	36	7.5	11.5	480	820	0	11.5+
A.K.	53	19	25	0.5	0	545	920	0	11.5+
C.H.	61	15	15	0	0	840	1,150	0.5	9.5+
E.B.	38	23	23	0	0	630	900	2.0	10.0+
E.B.	38	18	18	0	0	795	1,050	0	10.0+
B.F.	18	22	26	1.5	5.5	440	900	0	14.0+
A.V.	66	20	26	3.0	9.0	585	840	3.0	9.0+
A.C.	60	10	12	0	0	1,050	1,465	1.0	14.0+
E.F.	64	15	18	(0)	(0)	690	945	0	6.0
H.W.	43	24	29	0	6.0	1,255	1,570	0	6.0
C.M.	58	18	25	0	11.5	375	480	0	0.5
M.Me.	47	9	12	0	1.0	1,320	1,300	0	2.0
J.M.	45	10	22	2.0	11.0	735	1,170	0	6.0
A.Kn.	63	16	21	3.0	12.0	585	1,150	0	4.0
M.D.	21	9	13	1.5	8.5	945	860	0	0
C.Br.	64	17	20	2.0	5.5	565	820	0	4.5
A.E.	66	15	20	0.5	5.3	545	1,130	0	6.5
C.Bj.	70	17	26	14.0	15.5	375	565	3.5	20.5+
A.H.	47	16	19	0.5	2.5	305	735	2.5	11.5+
A.Re.	19	14	25	4.0	13.0	505	670	0	2.0
M.Mi.	72	18	18	0	0	585	860	0.6	5.6
Average		17.1	21.5	2.65		652	980	0.6	
Average maximum increase in respiratory rate		26%							
Average maximum increase in respiratory volume		51%							

## POSITIONING IN SURGERY OF THE EXTREMITIES

L. N. COZEN, M.D.,\* LOS ANGELES, CALIF.

*(From the Department of Orthopedic Surgery, College of Medical Evangelists)*

**S**URGICAL operations of the extremities are often more difficult than those of the abdomen. The principal cause of this increased difficulty is the relative inaccessibility of the incision on the extremity. Thus incisions on the mesial, lateral, and posterior surfaces of the arm or leg are not as easy to expose as the more infrequent anterior incisions.

Of distinct aid in operating is to tilt the patient in order to place the area for incision on a horizontal plane facing the ceiling. It may seem trite to speak of placing sandbags under the hip or shoulder, but such simple procedures are still frequently neglected, while the orthopedic surgeon sweats and strains.

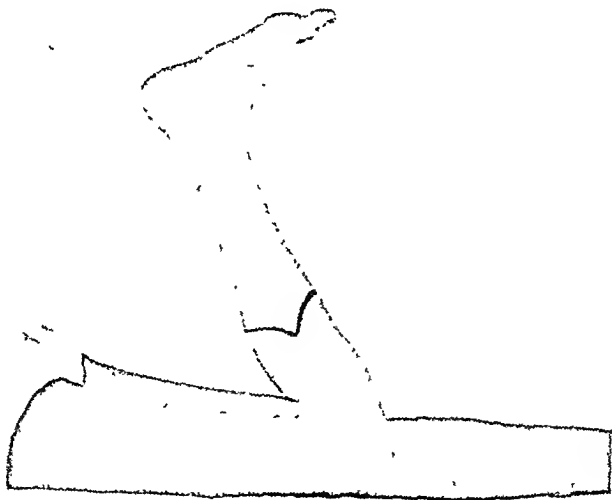


Fig. 1.—Position for lower leg amputations.

In operations of the tarsal region, such as in triple arthrodeses, facility will be increased by flexion of the patient's hip and knee in addition to rotating the hip joint externally or internally as the case may be.

Operations on the posterior aspect of the leg should be done with the patient prone on the table.

The force of gravity should be used whenever practical. This becomes applicable when exploring the various joints of the body. It is common

\*Major, Medical Corps, U. S. A. R.

Received for publication, June 30, 1941.

immediately afterward. In one case, the increase in rate persisted for more than thirty-five minutes. There were no significant changes of the pulse rate. None of the patients complained of any subjective ill effects.

Coramine in doses of 1.5 and 2 c.c. intravenously was given in eight cases. There was comparatively slight increase of rate and depth of respiration and no significant action upon the blood pressure and pulse in any of the patients without evidence of respiratory or cardiac depression; i.e., normal patients.

Three patients given saline solution intravenously in a control experiment showed no significant changes in rate or depth of respiration.

In the three cases of atelectasis which were studied, the administration of 0.48 Gm. of aminophylline intravenously at four-hour intervals was followed by the disappearance of the rhonchi and the symptoms incident to the bronchial obstruction. It must be stated, however, that other measures such as encouraging the cough reflex, steam inhalation, and postural drainage were also employed.

Aminophylline was given routinely at the University Hospital to sixty-nine cases of abdominal operation and in private practice to over 100 similar cases. Only three developed respiratory complications. This series is much too small to permit any conclusions. We hope to be able to report a larger series in the future.

#### SUMMARY

Intravenous administration of theophylline with ethylene diamine (aminophylline) increases the rate of respiration 26 per cent and produces an increase in depth of respiration approximately 51 per cent, when administered to normal individuals. There is comparatively a similar effect, but to a much smaller degree, when 2 c.c. of coramine is administered.

In view of these observations and favorable clinical impressions aminophylline in doses of 0.48 Gm. two or three times daily given in intravenous solution is recommended as a prophylactic measure for the prevention of postoperative respiratory complications. The procedure seems to have merit and warrants further investigation and clinical trial.

#### REFERENCES

- Askanazy, S.: *Klinisches Ueber Diuretin*, *Deutsches Arch. f. klin. Med.* 56: 209, 1895.  
 Binger, M. W.: Reducing the Risk of Operation for the Patient With Renal Disease, *S. Clin. North America* 20: 1187-1194, 1940.  
 Greene, J. A., Paul, W. D., and Feller, A. E.: Theophyllin With Ethylenediamine in Cardiac Failure, *J. A. M. A.* 109: 21, 1937.  
 Smith, Carter, and Sauls, H. C.: Preliminary Report Upon Intravenous Use of Theophylline With Ethylenediamine (Aminophylline) in Cardiovascular Disease and Bronchial Asthma, Atlanta, Ga. Unpublished report.  
 Council on Pharmacy and Chemistry: *J. A. M. A.* 108: 1887, 1937.

## POLYOSTOTIC FIBROUS DYSPLASIA

EDGAR H. WHITE, M.D., CINCINNATI, OHIO

*(From the Cincinnati General Hospital)*

SEVERAL recent case reports have called attention to multiple cystic bone lesions which do not fit into the usual classifications of bone disease and whose recognition as a definite clinical entity is now accepted. X-ray study of cystic bone lesions has led to numerous classifications, which, while helpful, are based on unsatisfactory and incomplete clinical and laboratory evidence in some instances.

The term cystic in this discussion is used to describe a circumscribed area of decrease in normal bone density in the roentgenogram, remembering that it is not easy to differentiate by x-ray between a true cyst filled with fluid and a circumscribed defect of bone filled with fibrous and osteoid tissue. If it can be generally appreciated that there exists a group of cases which may resemble, but whose etiology is in no manner related to, hyperparathyroidism, needless surgery may be avoided.

Jaffe in his very comprehensive and excellent treatise on hyperparathyroidism in 1933 in commenting on the cases of Hirsch, Willich, Bradfield, and Telford stated: "My impression is that these conditions are neither Recklinghausen's nor Paget's disease and that they constitute a still unidentified entity. I strongly suspect that they have a congenital basis."

In 1934 Freund reported the case of a girl 7 years of age who suffered a fracture of the right femur through cystic areas. This was followed by varus deformity and shortening. X-rays demonstrated typical multiple bone involvement with characteristic roentgenograms. Despite normal blood calcium and phosphorous levels, neck exploration was performed with negative results. This author arrived at several conclusions: (1) The lesion was primary in the diaphysis and not in the epiphysis or epiphyseal plate as in Ollier's disease. (2) The localized and generalized forms of osteitis fibrosa are separate entities. He discusses the possibility of aberrant embryonic tissue as the underlying etiological factor. (3) He pointed out again, as had Jaffe, that osteitis fibrosa was a nonspecific response to varying stimuli and that the duration, locations of lesions, and x-rays were the important factors in establishing the diagnosis.

Again in 1936 Meffert and Freund, discussing nongeneralized fibrous osteodystrophy, described three cases which revealed characteristic osteoporotic changes limited to monomelic rather than unilateral distribution. Blood chemistry in all cases was normal, and hyperostotic changes occurred only at site of fractures.

practice to allow the exposed knee joint to hang over the edge of the table, thus separating the joint surfaces. How often, however, is the same principle applied to the shoulder joint by placing the patient in a sitting position for operation? In this position the weight of the arm separates the shoulder joint surfaces. An added advantage of this position is the operator's ability to introduce instruments without the obstructing table to hamper him.

Surgical amputations are made easier by proper positioning of the patient.

For lower leg (tibial) amputations, the patient should lie prone on the table. With the posterior surface of his leg exposed, the important posterior tibial artery and nerve may be found and ligated. For the anterior portion of the incision and in order to ligate the anterior tibial artery and nerve, the surgeon flexes the knee. When a lower leg amputation is done with the patient supine, operating on the posterior portion of the leg becomes a gymnastic feat.

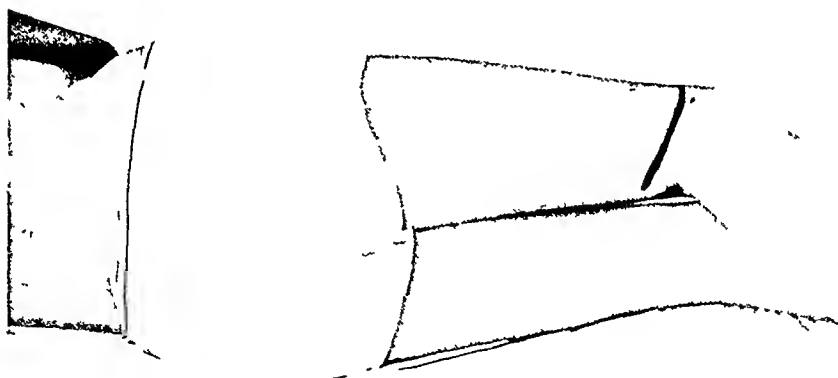


Fig. 2 —Position for thigh amputations

For thigh (supracondylar) amputations, the patient should lie on his sound side; thus, the important popliteal artery vein and common popliteal nerve face the operator. With the heel of the diseased leg resting on the table the hip joint can be rotated to expose anterior and mesial portions of the thigh.

#### SUMMARY

A frequently neglected measure in operations of the extremities is to place the patient in the correct position on the operating table. The correct position for each operation is that posture that renders the operative wound most accessible to the operator.

There was only twenty degrees of motion at the knee which the patient attributed to his unwillingness to flex this joint because of pain at the site of trophic ulcers over the tibial crest which had been present since 1937. Fig. 1 reveals two café-au-lait areas of pigmentation over the right flank posteriorly and over the dorsal spine just to the left of the midline.

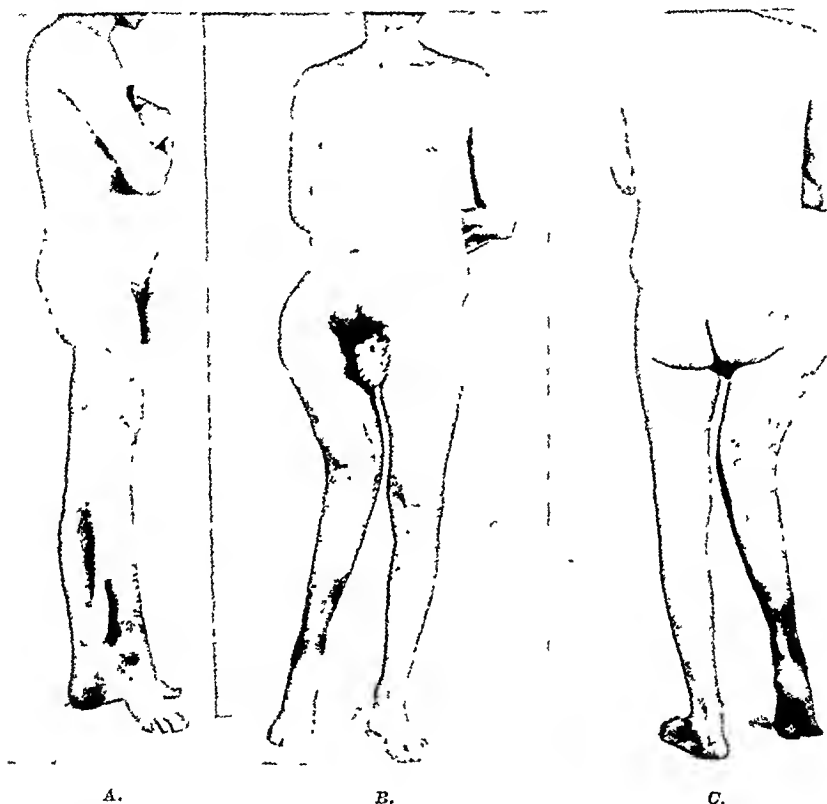


Fig. 1—Scar over greater trochanter site of surgery in 1903. Other incisions due to knee arthrodesis and biopsies. Notice the large superficial tumor in the region of the right posterior superior iliac spine. Areas of pigmentation along the left paravertebral and right chest wall are clearly visible. Pigmentation about right ankle due to vascular disturbances.

#### LABORATORY DATA

	CA	P	PHOSPHATASE
12/13/40	8.0 mg.	3.2 mg.	4.6 Bodansky units
12/14/40	7.0 mg.	3.2 mg.	5.6 Bodansky units
12/15/40	8.1 mg.		
12/23/40	9.0 mg.	3.2 mg.	4.4 Bodansky units
2/12/41	10.8 mg.	2.7 mg.	5.8 Bodansky units
2/14/41	11.2 mg.	2.5 mg.	6.5 Bodansky units

Kahn test, negative  
 CO<sub>2</sub> combining power, 51 volumes %  
 Urea N, 12 mg. %  
 N.P.N., 22 mg. %  
 Serum protein, 5.2%  
 Serum albumin, 2.3%  
 Serum globulin, 2.9%  
 B.M.R., -11

Albright and associates in 1937 described a syndrome in children characterized by skin pigmentation, precocious sexual development in the females, disseminated osteitis fibrosa cystica, normal blood chemistry, and no evidence of parathyroid adenomas. While the reported cases since this paper have been chiefly male adults, there has been no history of sexual precocity. I have examined Campbell's case of a young adult, and it appears probable that adequate follow-up of children and young adults will reveal a status approximating the more recently described adult cases.

To Lichtenstein in his classical paper in 1938 must be given credit for the name which is simple and from both x-ray and microscopic viewpoints accurate, polyostotic fibrous dysplasia. His excellent review and series of eight cases leave little doubt that there are individuals who in the past have been diagnosed as having hyperparathyroidism and Ollier's disease who belong to this entity.

In 1939 Horowitz and Cantarow described a male with a nine-year follow-up who showed increasing deformity of both femora. X-rays and biopsy were characteristic.

Moehlig and Schreiber in 1940 described a 16-year-old boy with a mass in the right occipital region. The right femur, ilium, tibia, and fibula as well as the skull were involved. Interestingly enough, there were changes in secondary sex characteristics, puerile breasts and feminine voice being notable.

#### CASE REPORT

A white male, 57 years of age, entered the Cincinnati General Hospital on Dec. 11, 1939, because of pain, swelling, and disability of the right knee. He gave a history of having fallen in 1903, suffering a fracture of the right femur in the upper third. An immediate open reduction was done and a "wedge" of bone resected for correction of existing deformity. An uneventful convalescence followed, but upon beginning weight-bearing he noticed that there was considerable lateral bowing of his thigh.

In 1923 he began to observe soft, painless masses in the upper two-thirds of the right thigh and around the right hip laterally and posteriorly. At this period they were fluctuant and could be moved under the skin; later they became firm, "like a rubber ball," and fixed. During the past five years many other such tumors have appeared, and for the past ten to fifteen years there has been a progressive lateral bowing of the right thigh and shortening of the extremity. Since 1928 he has had pain of increasing severity in the right knee, but he managed to continue to work until five days before this hospital admission.

Examination revealed the right thigh to be approximately 25 per cent larger than the left with marked lateral and anterior bowing of the femur as seen in Fig. 1. There was shortening of 7 cm. of the right lower extremity, limited entirely to the femur.

The increase in circumference of the thigh was due to numerous discrete, nontender, movable masses of firm consistency, extending from the level of the knee to the crest of the ilium, involving both buttocks and paravertebral regions at the lumbar level. These varied in size from 1 by 1 cm. to 8 by 10 cm. The larger were fluctuant, all were more or less movable, and none were fixed to the skin.

3. *Pain*.—Lichtenstein and others believe that pain is common, especially in the hip. This appears to be reasonable upon consideration of the marked femoral deformities with alterations in the femoral head and development of secondary acetabular arthritis demonstrable on the x-rays of this and other reported cases. Disregarding that pain, which can be explained on the basis of joint derangement and arthritis, a possible explanation may be found in the dull ache experienced by patients with Paget's disease. Cortical expansion is common to both, and the pain likewise may be of periosteal origin.

4. *Deformities*.—With a material reduction of cancellous bone and particularly in those instances where medullary bone is completely replaced by fibrous tissue throughout the diaphysis, deformities of bones of the lower extremities are to be expected. Since a small amount of cortex is sufficient to prevent changes in the small bones, gross malformations are encountered in the long bones and particularly the femur. Lateral and anterior bowing of the femur, coxa vara, genu valgum, and pes valgus are most often encountered. Any alteration in shape is secondary to stress and weight placed upon abnormal bone and is not an intrinsic part of the disease as seen in Ollier's disease where disturbances in epiphyseal plate development result in growth abnormalities. Shortening of the lower extremity may be extreme, although Freund and others have reported an increase in length of the involved leg.

5. *Fractures*.—While there was adequate trauma in this case and in other reports to explain the fractures of the femoral shaft, it is to be expected that pathologic fractures would be prevalent. It is remarkable that not more have been encountered in this case after consideration of the x-rays. While there are no reports of fractures in bones other than the femur, there seems to be no tendency to nonunion.

6. *Sexual Changes*.—Sexual precocity was an early and invariable manifestation in Albright's cases and in all other reports to which he refers except that of Campbell's. Freund's patients, who were at puberty or older, did not display similar changes, and there is no mention of precocious sexual development in recent years in the literature with the exception of Moehtig and Schreiber's report of a young male who had feminine breasts, puerile voice, absence of beard and axillary hair, and feminine distribution of pubic hair. Marked thickening of all the bones of the base of the skull is present in this case without alteration in primary or secondary sex characteristics.

7. *Subcutaneous Tumors*.—That this was a case of extreme severity with advanced lesions was evidenced by the presence of numerous masses of varying size lying in the subcutaneous tissues of the right thigh, lateral aspect of the right hip, both buttocks, and over the sacrum and lumbar spine. These tumors varied from 1 by 1 cm., to 8 by 10 cm. in size. They were firm, well encapsulated, freely movable, nontender, and



Over a six-day test period this patient was in slight negative calcium balance.

X-rays showed involvement of all bones of the right half of the body, the right foot, upper and lower leg, entire right half of the pelvis, hand, arm and forearm, skull and mandible being implicated. Other than lesions in the left ilium, left hand, left half of the mandible, and base of the skull, the left half of the body was uninvolved.

On Feb. 17, 1940, biopsy was performed with removal in toto of a 3 by 2 cm. sized cyst from the anterolateral aspect of the right lower thigh. Upon incising the fascia lata it was obvious that there was complete alteration of the normal muscle, fascial and articular tissue. There was almost complete replacement of muscle bellies by lobular masses of varying sizes with total disorganization of the normal fascial planes. The cyst was easily shelled out by blunt dissection during which there was a conspicuous absence of bleeding.

Pathologic report on the cyst wall stated that it consisted of fibrous tissue with a small amount of elastic tissue interspersed. The contents were described as gelatinous, mucoid, transparent, yellowish material with no evidence of cellular inclusion. The final opinion was that there was a close resemblance to a ganglion.

High thigh amputation was requested by the patient, but because of the technical difficulties of the fitting of a prosthesis, hip disarticulation or knee fusion was all that could be considered. On April 16, 1940, a Hibbs' arthrodesis of the right knee was done despite the prediction that little hope for bony union was entertained after consideration of the reduced amount of cortical bone. To date there has been no clinical or x-ray evidence of osseous union.

A second biopsy was done on Aug. 3, 1940, at which time two additional soft tissue tumors 3 by 4.5 cm. were shelled out and a piece of cortical and medullary bone from the midportion of the femur obtained. The femoral shaft was found to be considerably enlarged and uniformly irregular. There was no evidence of cortical bone defects, but the cortex could be penetrated easily by a blunt instrument. Inspection of the medullary cavity revealed that there was complete replacement of normal cancellous bone by cystic masses of varying sizes resembling those encountered in the thigh. Small amounts of granular material were palpated which were probably the remnants of the bone trabeculae. Throughout the procedure, little or no bleeding was encountered. The microscopic diagnosis from a competent pathologist was an aberrant form of hyperparathyroidism.

#### CLINICAL FEATURES

1. *Age of Onset.*—As in the above case, the physician frequently is consulted because of mechanical difficulties when the patient is middle-aged or older. Severe cases in children are exceptions. The onset of the lesions before the age of 10 years followed by a long, protracted, benign course which extends over years is characteristic.

2. *Skin Pigmentation.*—While there was no evidence of skin pigmentation reported in any of Lichtenstein's eight cases, Albright placed particular emphasis upon this feature, believing it to be a cardinal clinical sign. Goldhamer also mentions an increase in the melanin content of the skin. While there is a suggestion of peripheral nerve distribution on the right chest wall of this case, the vertical paravertebral location on the left side disclaims any neurological relationship. The dermatological manifestations do not suggest the type of skin pigmentation seen in neurofibromatosis.

The diaphysis is characteristically widened, and with severe involvement such increase may be great. These changes are understandable after consideration of the atrophy and thinning of the cortical bone. X-rays of bones in which fractures have occurred reveal adequate callus of periosteal origin with evidence of periosteal new bone being present without exception. There is no evidence of interruption of continuity of the cortical bone.

The areas of rarefaction are of varying size, and in many instances possess indefinite outlines coalescing in such a manner that a large section of the bone appears to be generally decalcified. Trabeculation is not a prominent feature, but occasionally thin, delicate trabeculae are noted. These thin, indefinite trabeculations bear little resemblance to those seen in giant-cell tumor or localized osteitis fibrosis cystica.

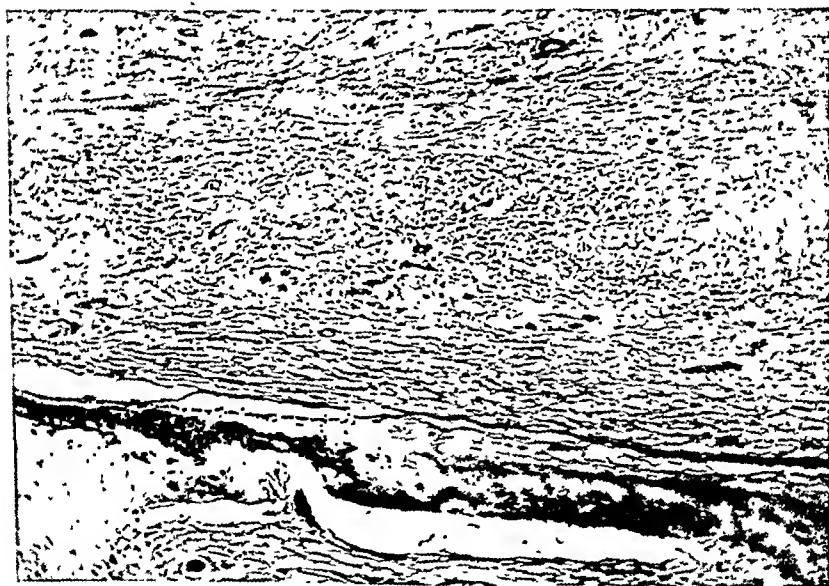


Fig. 2—Cortical bone is atrophic but without a break in continuity. Notice the tremendous thickening of the periosteum with marked increase in connective tissue overlying the periosteum. Endosteum is not discernible.

The femur is the bone most commonly involved, followed in order by the pelvis, tibia, humerus, radius, ulna, small bones of the hands and feet, and skull.

With extension of the cystic areas into the femoral head and condyles, deformities secondary to weight-bearing are common. Coxa vara, varus deformities of the femoral shaft, genu valgus, and anterior bowing of the tibia are encountered. Contralateral bones which are not involved maintain normal density; this is an important diagnostic point when considering hyperparathyroidism. Roentgenograms of some of the published cases reveal sclerosis, particularly of the tibia.

unattached to the skin. Arrangement was haphazard with no attempt at distribution along peripheral nerves, some crossing midline. In some instances these masses were immediately beneath the skin and superficial to the fascia. In addition there were innumerable similar lesions in the intermuscular fascial planes and in many instances imbedded directly in the muscle bellies to such an extent that there was almost complete replacement of the thigh musculature. Biopsies of the cysts on two occasions revealed similar microscopic findings identical with those of the cystic masses removed from the medullary canal of the femur.

Two explanations are suggested: (1) Biopsy revealed the cortex of the femur to be paper thin, and it is possible that a minute cortical defect may have existed with escape of medullary canal contents. The widespread distribution to the subcutaneous level, the encapsulated nature of the tumors, and the findings of an intact periosteum are incompatible with such an explanation. (2) As will be explained later, it is generally believed that this disease is based upon a congenital abnormality in fibrous tissue maturation and development.

#### X-RAYS

The characteristic location and appearance of the roentgenograms are the most valuable and important of all clinical or laboratory evidence. While most writers describe unilateral lesions, there seems to be no valid reason why such an arrangement should always exist. In severe cases, particularly in children, bilateral lesions are present, as reported by Albright. Involvement was predominantly unilateral in the patient reported here, but both ilia and hands were affected with suggestive areas of rarefaction in the long bones on the left side.

The roentgenograms characteristically exhibit multiple areas of decreased density involving the entire or major portion of the diaphysis, stopping at the epiphyseal plate in children and extending to the articular cartilage in adults. Partial involvement of the diaphysis of long bones is unusual in contradistinction to the findings in cases of giant-cell tumor, osteitis fibrosa cystica localisata, xanthomatosis, and Ollier's disease. Extension from articular cartilage to articular cartilage without permitting interspersions of areas of normal bone depends upon the age of the patient and the duration of the disease, rarely being encountered before puberty and consistently thereafter.

Scattered among the cystic lesions are areas of increased density. These are irregular, are variable in size and density, and assume haphazard patterns. The outlines of these areas are hazy and exhibit no reactive peripheral zone. There is a close resemblance to osteopoikilosis, the lesions in the os calcis being most suggestive.

## PATHOLOGY

*Gross Pathology.*—The subcutaneous tumor masses at biopsy were found to be grayish, glistening cysts with translucent walls. These were easily shelled out of the subcutaneous tissue and fascial planes by blunt dissection. The size varied from several millimeters to 8 to 10 cm. in diameter. There was actual contact by the cysts with the periosteum at many points. The contents of these cysts was a thick, gelatinous, mucinous material closely resembling the contents of a ganglion.

The cortical bone was paper thin and yielded easily to a blunt instrument. There was marked alteration in the appearance of the periosteum, being 2 to 4 mm. thick, boggy, and indurated. The normal glistening appearance was replaced by a dull, whitish, lusterless tissue somewhat

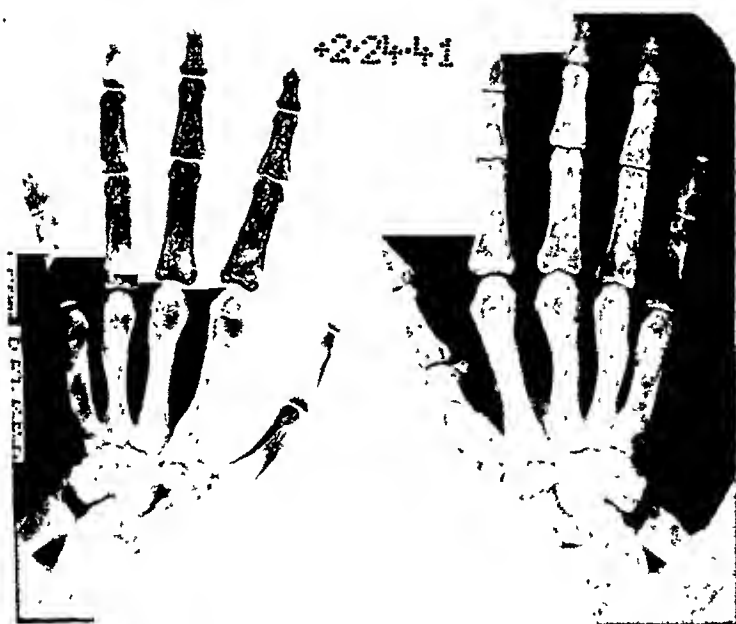


Fig. 5—Both hands are involved, the right more than the left. The right hand shows all bones affected along with expansion of the metacarpals.

resembling scar tissue. Attempts to elevate the periosteum revealed it to be abnormally friable and without the usual periosteal bleeding. Raising of a trap door of cortical bone disclosed the medullary canal to be completely replaced by gelatinous tissue closely resembling the cystic material encountered in the soft tissues of the thigh.

It is now generally appreciated that the microscopic picture of fibrous tissue replacement of medullary bone with absorption of bone trabeculae is not a specific response to any single etiological factor or disease. Osteitis fibrosa is seen in hyperparathyroidism, localized osteitis fibrosa



## DIAGNOSTIC AIDS

The values for blood serum phosphorus and calcium in this case and in all those reported have been within normal limits. There have been a few instances where the calcium values approached the upper limits of normal without apparent significance.

The phosphatase level has shown slight elevation on occasion in this case. Freund and Lichtenstein reported cases showing phosphatase elevation as high as thirty-two units. Such elevation has been adequately proved to depend upon new bone production. In polyostotic fibrous dysplasia there is some capacity for new bone formation and, as has been shown on x-ray, this is chiefly periosteal.



Fig 7—The entire right half of the pelvis, all of the sacrum, and the crest of the left ilium are involved. Absence of lesions in the lumbar spine is notable.

## PATHOGENESIS

It is obvious that we are dealing with an inherent disorder of fibrous tissue rather than alterations in bone secondary to extraosseous factors. Those cases which have been carefully followed date the onset of the disease to childhood or earlier. Albright's youngest case was 3½ years of age. Certainly the characteristic onset before the age of 10 years followed by a long, chronic, slowly progressive course strongly suggests congenital etiology. There are few skeletal lesions whose duration extends over decades and whose character is essentially benign despite

cystica, neurofibromatosis, callus following fracture, Paget's disease, osteomalacia, rickets, and chronic inflammatory diseases of bone.

Jaffe and Lichtenstein, who have had an opportunity to examine the most pathologic material, have described thinning of the cortical bone which they believe is due partially to absorption but chiefly to erosion of the endosteal surface by the proliferating fibrous tissue. There have been no descriptions of endosteal new bone formation, and this agrees with the microscopic findings of our biopsies. There was no evidence of penetration of the cortex by fibrous tissue in these specimens.

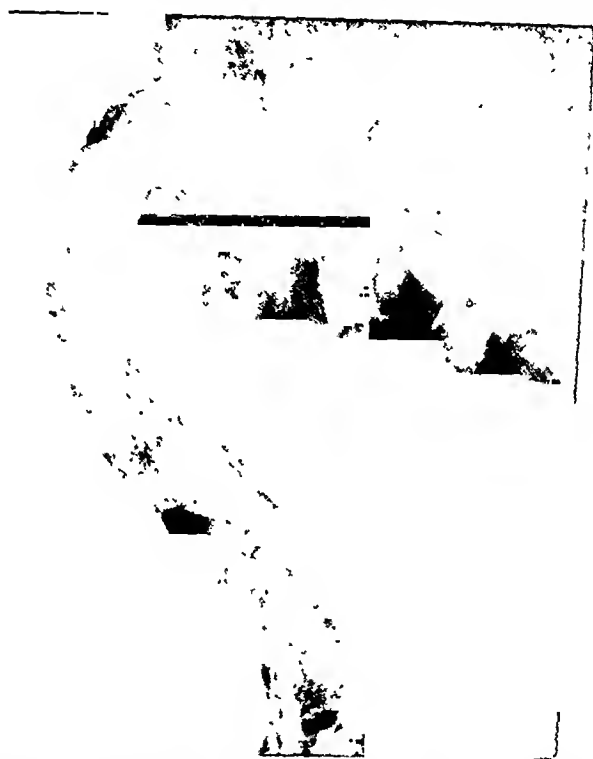


Fig. 6.—The location of lesions throughout the entire length of the femur is characteristic. The shaft is moderately expanded and the cortex reduced throughout. The defect in the cortex on the lateral aspect is the site of biopsy.

There has been almost complete replacement of medullary bone by fibrous tissue in this case and in the photomicrographs reproduced by Jaffe and Lichtenstein. Some sections (Figs. 3 and 4) reveal considerable replacement, while elsewhere bone trabeculae show less absorption. The fibrous tissue encountered differs in no way from that seen in osteitis fibrosa in other lesions. The bone trabeculae appeared to possess no definite pattern and stained poorly. Osteoclasts were not seen. There was no evidence of giant cells or cartilage. Vascularity was surprisingly rich.

concomitant advanced pathologic changes that can be accounted for other than on a congenital developmental abnormality. The presence of numerous cystic masses outside bone which possess no clinical or microscopic evidence of malignancy seem to be best explained upon a congenital aberration of primitive fibrous tissue. The similar gross and microscopic resemblance between the fascial and osseous lesions would indicate a common genesis. The unilateral distribution of the lesions precludes the possibility of endocrine or hormone etiology, as does the presence of normal, unaffected bones on the opposite side.



Fig. 10.—Thickening of the basilar portions of the occipital, temporal, and sphenoidal and frontal bones is characteristic. Notice the encroachment on the sella turcica. Involvement of both sides of the mandible is discernible.

#### DIFFERENTIAL DIAGNOSIS

1. *Hyperparathyroidism.*—The superficial resemblance of the roentgenograms of the lesions of polyostotic fibrous dysplasia to hyperparathyroidism has created confusion, and in most instances has been described under hyperparathyroidism, as evidenced by numerous reports of surgical exploration of the parathyroid glands without encountering adenomas.

Before the establishment of hyperparathyroidism as a distinct clinical entity it was appreciated by Freund, Hunter, and Turnbull and Jaffe that there were cases of cystic bone lesions which were not explainable on an endocrine imbalance. This fact unfortunately is not generally appreciated today despite recent authoritative articles.

As has been emphasized already, if x-ray examination is confined to a single bone or to a portion of an extremity or if the diagnosis has been



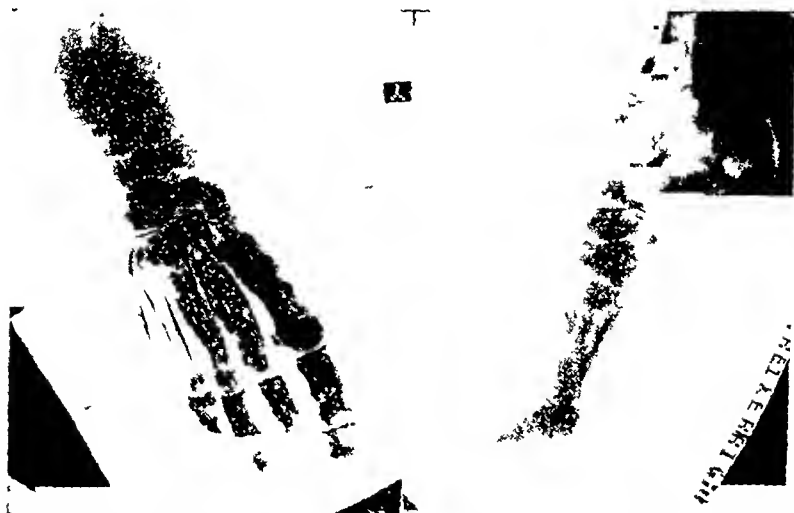


Fig 8—Expansion of the metatarsals and phalanges more marked than in the hand with maximum changes to be noted in the medial portion of the foot. Notice the well-defined areas of sclerosis in the os calcis and lower ends of tibia and fibula



Fig 9—The knee region density intermingled with the plate acting as a barrier, extending to the combination of areas of increased density

the combination of areas of increased density is no evidence of the epiphyseal level being evident

shaft or center of the diaphysis is usually uninvolved. Clubbing of the metaphysis with longitudinal areas of sclerosis alternating with areas of decreased density are in contrast to the uniform expansion of the entire shaft as seen in fibrous dysplasia. Severe deformities subsequent to alterations in the epiphyseal cartilage are more common in Ollier's disease.

#### PROGNOSIS AND TREATMENT

The prognosis of polyostotic fibrous dysplasia for normal life expectancy apparently is excellent. Deformity and disability, especially of the lower extremities, is common, and while these patients may continue to be active for many years without discomfort, they may ultimately seek medical aid for mechanical difficulties.

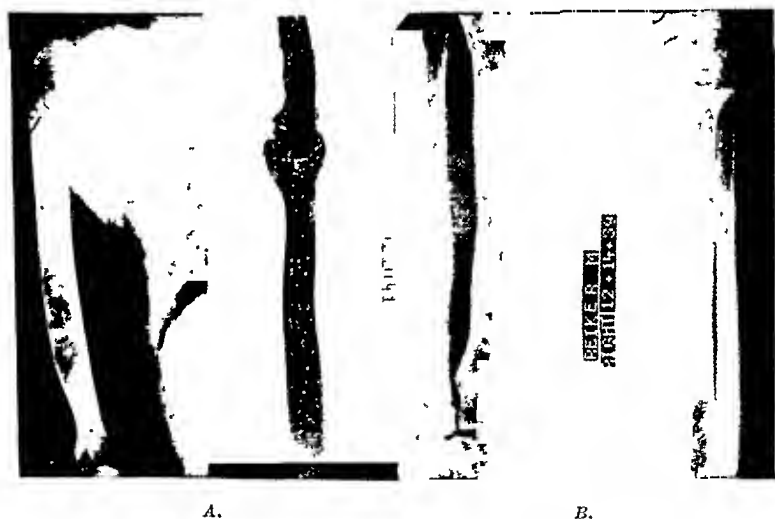


Fig. 12—While the entire humerus, radius, and ulna are involved, the cystic appearance is less marked, particularly in the ulna. Gross deformities are nonexistent in contrast to the lower extremities.

Up to the present there has been no report of nonunion following a fracture nor any evidence on a clinical or microscopic basis for malignant transformation of any of these lesions.

While there have been alterations in secondary sex characteristics in young female patients, adult patients of both sexes have not been noteworthy in this respect.

Lichtenstein believes that the phosphatase level is of value in estimating surgical prognosis and that little evidence of new bone formation exists when phosphatase values are within normal limits. The extent of involvement, the amount of cortical expansion, and residual bone cortex should determine the patient's fitness for surgical procedures rather than the phosphatase level. Alterations in other bones with abortive

made on biopsy alone, serious errors will occur. The microscopic pathology of hyperparathyroidism and Ollier's disease is closely similar but nonspecific, and it is obvious that limited x-ray examination would result in roentgenograms which would be confusing. Polyostotic fibrous dysplasia with its onset at or before puberty, long, protracted course, normal blood calcium and phosphorus values, and characteristic unilateral distribution of lesions creates a well-defined syndrome. The presence of bones of normal contour and density on the unaffected side in a patient with multiple cystic lesions along with areas of skin pigmentation and multiple subcutaneous nodules of varying sizes should be helpful in ruling out generalized osteitis fibrosa cystica.



Fig. 11—The entire lengths of both tibia and fibula are implicated. There is only moderate bowing despite considerable loss of cortical bone. Notice that there are no areas of normal bone existent.

2. *Ollier's Disease*.—Dyschondroplasia with its resultant deformities presents x-rays so characteristic that differentiation should not be difficult and biopsy would appear to be rarely necessary. The lesion is primarily localized to the epiphyseal plate in Ollier's disease, and as expected, the metaphysis and juxtaepiphyseal areas are the sites of maximum pathologic changes. Unlike polyostotic fibrous dysplasia, the

18. Meffert, C. B., and Freund, E.: On the Different Forms of Non-Generalized Fibrous Osteodystrophy, *Surg., Gynec. & Obst.* 62: 541, 1936.
19. Moehlig, R. C., and Schreiber, F.: Polyostotic Fibrous Dysplasia, *Am. J. Roentgenol.* 44: 17-23, 1940.
20. Priesel, R., and Wagner, R.: Osteodystrophia Fibrosa, *Acta. paediat.* 11: 237, 1930.
21. Robson, K., and Todd, J. W.: Fibrocystic Disease of Bone With Skin Pigmentation and Endocrine Dysfunction, *Lancet* 1: 377, 1939.
22. Salzer, H.: *Wien. klin. Wchnschr.* 46: 862, 1933.
23. Snapper, I., and Parisel, C.: *Quart. J. Med.* 2: 407, 1933.
24. Stalman, A.: *Virchows Arch. f. path. Anat.* 289: 96, 1933.
25. Summerfeldt, P., and Brown, A.: Osteodystrophia Fibrosa. Case Report, *Am. J. Dis. Child.* 57: 90, 1939.
26. Telford, E. D.: A Case of Osteitis Fibrosa, *Brit. J. Surg.* 18: 409, 1931.
27. Weil: *Klin. Wchnschr.* 1: 2114, 1922.
28. Willich, C. T.: Spontaneous Healing of a Case of Generalized Osteodystrophy Fibrosa, *Beitr. z. klin. Chir.* 146: 103, 1929.

attempts at new bone formation may elevate the phosphatase level and lull the surgeon into a false sense of security. Surgery on any bone which is severely involved should be considered only as a final resort. It is probable that new bone formation is more active in young patients as all reported fractures in this age group healed promptly. Amputation or the employment of braces in severe deformities of the lower extremities would appear to be more satisfactory than attempts at arthrodesis or surgical correction of deformities.

#### SUMMARY

1. Polyostotic fibrous dysplasia is a definite clinical entity with characteristic roentgenograms.
2. Differentiation from hyperparathyroidism is essential in view of more favorable prognosis and nonsurgical management.
3. Additional evidence indicating origin from fibrous tissue dysplasia is presented.
4. Reconstructive surgery on involved bones does not appear to be warranted.

I am indebted to Dr. Joseph A. Freiberg, of the Cincinnati General Hospital, for assistance in preparing this article.

#### REFERENCES

1. Adams, C. O., Compere, E. L., and Jerome, Jerome: Regional Fibrocystic Disease, Surg., Gynec. & Obst. 71: 22, 1940.
2. Albright, Fuller, Butler, A. M., Hampton, A. O., and Smith, Patricia: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction With Precocious Puberty in Females. Report of Five Cases, New England J. Med. 216: 727, 1937.
3. Albright, Fuller, Seoville, B., and Sulkowitch, H. W.: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and a Gonadal Dysfunction. Report of Two More Cases, Endocrinology 22: 411, 1938.
4. Borak, J., and Doll, B.: Wien. klin. Wchnschr. 47: 540, 1934.
5. Braid, F.: Osseous Dystrophy Following Icterus Gravis Neonatorum, Arch. Dis. Child. 7: 313, 1932.
6. Braid, F.: Generalized Osteitis Fibrosa With Areas of Pigmentation of the Skin and Precocious Puberty in the Female 14: 181, 1939.
7. Freund, E.: Osteodystrophy Fibrosa Unilateralis, Arch. Surg. 28: 849, 1934.
8. Gaupp, V.: Monatschr. f. Kinderh. 53: 312, 1932.
9. Goldhamer, K.: Fortschr. a. d. Geb. d. Röntgenstrahlen 49: 456, 1934.
10. Goldhamer, K.: Wien. klin. Wchnschr. 47: 218, 1934.
11. Hirsch, I. S.: Generalized Osteitis Fibrosa, Radiology 13: 44, 1929.
12. Horowitz, R., and Cantarow, A.: Polyostotic Fibrous Dysplasia, Arch. Int. Med. 44: 280, 1939.
13. Hummel, R.: Two Cases of Juvenile Paget's Disease, Röntgenpraxis 6: 513, 1934.
14. Hunter, D.: Generalized Osteitis Fibrosa, Brit. J. Surg. 19: 203, 1931-1932.
15. Lichtenstein, L.: Polyostotic Fibrous Dysplasia, Arch. Surg. 36: 874, 1938.
16. McCune, D. J.: Osteitis Fibrosa Cystica. Case of Nine Year Old Girl Who Also Exhibits Precocious Puberty, Multiple Pigmentation of the Skin and Hyperparathyroidism, Am. J. Dis. Child. 52: 743, 1936.
17. McCune, D., and Bruch, H.: Osteodystrophia Fibrosa. Report of a Case in Which the Condition Was Combined With Precocious Puberty, Pathologic Pigmentation of the Skin and Hyperthyroidism With a Review of the Literature, Am. J. Dis. Child. 54: 806, 1937.

C. PARTURITIONAL TORTICOLLIS (Cases Occurring During Delivery).—This group is included under congenital torticollis because of custom, but it is really a distinct class in itself. It is the commonest form of congenital torticollis and is more amenable to surgical therapy than is any other type. The term parturitional is suggested because this type does not occur before delivery but is noticed a few hours to a few weeks after delivery. The pathologic lesions may be classified as follows: (1) rupture of the sternomastoid muscle, (2) hematoma of the sternomastoid muscle with subsequent fibrosis, and (3) combinations of the rupture and hematoma. This type, parturitional torticollis, is the one referred to as being affected by the scalenus anticus muscle.

3. *Functional Torticollis*.—A peculiar type that does not reveal any organic muscular spasm or contraction. It may be necessary to immobilize the neck by means of a plaster of Paris jacket or a corrective brace. A satisfactory brace is one described below (Fig. 2). The prognosis for complete cure is excellent.

4. *Spasmodic Torticollis*.—This form is characterized by clonic spasms of the sternomastoid plus other cervical muscles, particularly those in the suboccipital triangle. An encephalitis is usually considered to be an initiating factor. The prognosis is not favorable as to cure. Operations on the spinal accessory nerve as well as the fifth, sixth, and seventh cervical nerves and various myotomies have been advocated.

According to the above classification, there are many types of torticollis of which the acute acquired torticollis or "stiff neck" is the most frequent. However, this type is of slight clinical and surgical significance because it is very transitory. The next commonest type is parturitional torticollis which heretofore has been termed congenital torticollis. When these patients are operated upon, it has been observed that the sternomastoid muscle per se is shortened and contains a preponderance of scar tissue, so much so that large patches of blanched fibrous tissue replace the normal muscle tissue. Adhesions, quite dense at times, exist between the capsule of the muscle and the muscle proper. Other soft parts of the neck may be adaptively shortened. These changes impress one as being due to a fibrous myositis and perimyositis, and with a history of occurring shortly after delivery, it is reasonable to assume that it is of traumatic origin. The usually employed operative procedure to correct this lesion is section of the sternomastoid muscle and all adhesive bands. This procedure has met with both success and failure, some deformities being overcome while others persisted. The explanation for this is not clear, but from the case histories described below one will observe that the scalenus anticus muscle may have played a cardinal role in perpetuating the deformity in those cases that did not respond to sternomastoid myotomy alone.

CASE 1.—Master G. M., 14 year old white male (Fig. 1), was admitted to the Touros Infirmary on April 21, 1938, with a chief complaint of "crooked neck."

## THE SCALENUS ANTICUS FACTOR IN CONGENITAL TORTICOLLIS

SIDNEY M. COPLAND, M.D., NEW ORLEANS, LA.

(From the Department of Surgery, Touro Infirmary)

CONGENITAL torticollis, although known for centuries, remains a therapeutic enigma at the present and the multiplicity of operative procedures advocated for this entity serves as a mute witness to this fact. Torticollis, in general, is characterized by an involvement of the sternomastoid muscle, although at times other cervical muscles are involved, in which the muscle undergoes a contraction resulting in its overaction and thereby causing a deformity. This condition is unilateral in the majority of cases; however, a bilateral type does occur rarely. Recently, it has been my experience while operating upon two successive cases of congenital torticollis, to encounter a factor not heretofore mentioned; namely, the scalenus anticus muscle as being partly responsible for the deformity. This observation was first noticed during the course of the operation and when it was seen again in a few weeks, its importance was emphasized. Since these two cases were seen, a third case has presented a similar picture.

Because the discussion of the role of the scalenus anticus muscle is limited to certain types of torticollis, and wishing to avoid confusion, a classification of torticollis in general is presented.

### TORTICOLLIS

1. *Acquired Torticollis*.—This is the commonest form of torticollis and is usually termed a "stiff neck." It is a myositis of the sternomastoid, occasionally the trapezius, due to exposure or changes in temperature. Although self-limited, heat therapy is of benefit.

2. *Congenital Torticollis*.—This is subdivided into three groups as follows:

A. PRIMARY CONGENITAL TORTICOLLIS.<sup>1</sup>—This type is invariably caused by an embryonic defect and is present long before delivery. It is due to one of the following: (1) synostosis of atlas and axis, (2) fusion of atlas and occiput, (3) malformation of cervical vertebrae, or (4) cervical rib.

B. SECONDARY CONGENITAL TORTICOLLIS.—This type fails to reveal any basic anatomical deficiency but definitely antedates birth and is present at time of delivery. There is no adequate explanation of the phenomenon, but it has been theorized that an abnormal position of the fetal head in utero may be the reason.

<sup>1</sup>Received for publication, June 23, 1941.

the muscle exposed. The two muscle heads were dissected free from the posterior muscle capsule and severed in an oblique direction. No bleeding was encountered in the muscle proper. The posterior muscle sheath was then divided. An unsterile assistant now placed the head in overcorrection and it was noted that there was some inhibitory factor preventing overcorrection. The wound was palpated and a tense, thick, spastic mass was palpable. This proved to be the scalenus



Fig. 2—Case 1, after operation and after body cast has been removed. Patient wearing postoperative brace of author's design.



Fig. 3—Case 1, six months after operation. Compare with Fig. 1.

anticus muscle. The transverse colli artery was retracted, the pre-scalenus fat was dissected, and the muscle exposed. The phrenic nerve was visualized on the anterior surface of the muscle and retracted medially. The sixth and seventh cervical nerves were seen lateral to the muscle. The muscle appeared to be tense and hypertrophied. An interior scalenotomy was done following which the unsterile assistant was able to place the head in extreme overcorrection. With the head in this position, digital palpation failed to reveal any further constricting structures. The wound was closed in layers.



This complaint had been present since infancy. The physical examination showed a marked inclination of the head toward the left shoulder, the chin pointing toward the right. The right side of the face was larger than the left. The sternomastoid muscle on the left was very spastic and its anterior border on touch seemed as if it was a taut rope. The motion of the head was very limited in all directions and the deformity could not be corrected either actively or passively. The scapula on the affected side was more elevated than the other. The remainder of the physical and laboratory examinations were essentially negative. The x-rays

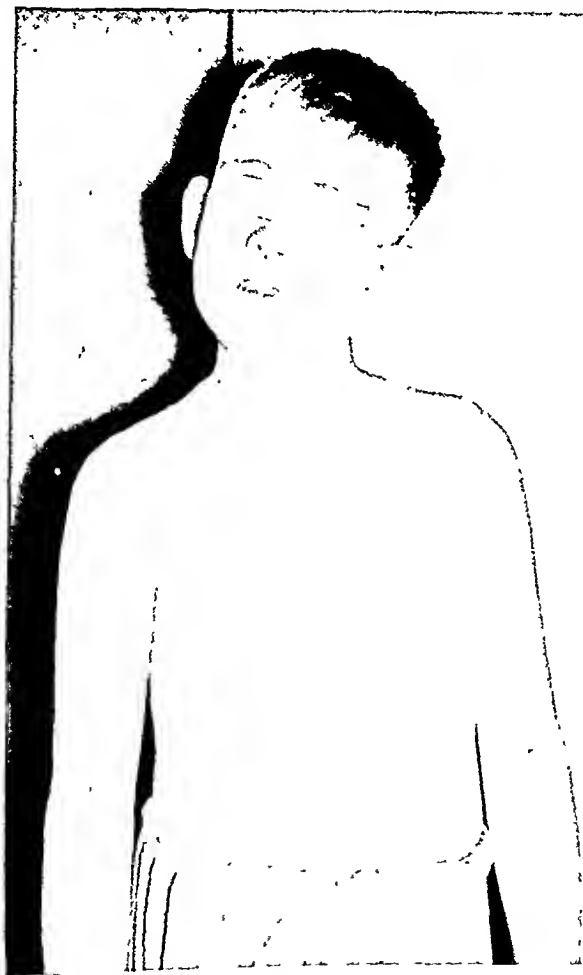


Fig. 1.—Case 1, before operation.

of the head and neck did not reveal any osseous deformities. Parturitional torticollis was considered the most likely diagnosis. Operation was performed on April 22, 1938, under a general anesthetic. A curved incision, one inch above the left to just beyond the posterior border, was made. The incision extended through the skin. The flap, the subcutaneous tissue, and platysma muscle were dissected upward en masse. It was necessary to ligate the external jugular vein. The anterior capsule of the sternomastoid was incised and the sternal and clavicular heads of

head was turned to the right and the chin pointed downward. A hemiatrophy of the right half of the face was present. The operation as described in Case 1 was performed and a hypertrophy of the scalenus anticus muscle was present. However, it was necessary to expose this muscle before concluding it was hypertrophied for palpation was not as definitely indicative as in the above two cases. A microscopic examination of the muscle revealed large amounts of fibrous connective tissue. The postoperative course was uneventful; a body cast was worn for six weeks followed by corrective exercises and a brace for six months. At the time of operation, the patient was a messenger boy and had obtained this position only through influence. Since operation, he has held better positions in industrial plants and has passed physical examinations to obtain the two positions without any difficulty (Fig. 6).



Fig. 5.—Case 2, six months after operation. Compare with Fig. 4.

At the operation in Case 1 it was evident that the scalenus anticus muscle played a role in maintaining the deformity, and when a short time later a second case was observed with a similar pathologic picture, it suggested that the condition occurs not infrequently. The third case was noted because my former experience made me determined to expose the scalenus anticus muscle routinely in this type of operation. The *modus operandi* of the scalenus anticus factor was not clear at first, but when the anatomy and function of this muscle was studied, the probable mechanism becomes evident.

Morris<sup>2</sup> described the function of the scalenus anticus as follows: "With the thorax fixed, the scalene muscles bind the neck to the side and slightly forward and turn it slightly towards the opposite side." Deaver<sup>3</sup> stated: "The anterior scalene muscle, when acting from its point of origin, will raise the first rib, but if the rib be fixed, the muscle acting from below will flex the lower cervical vertebrae, at the same time slightly rotating these vertebrae." The scalenus anticus muscle arises from the anterior tubercle of the transverse process of the third,

The patient's head was then placed in overcorrection and a body east applied from waist to forehead. The patient left the operating room in good condition. He was discharged from the hospital four days later; the maximum temperature during his hospital stay was 99° F. In six weeks the east was removed and a special correction brace was applied (Fig. 2). Corrective exercises were also instituted. A very satisfactory result has occurred (Fig. 3). The patient is able to swim and play ball for the first time in his life.

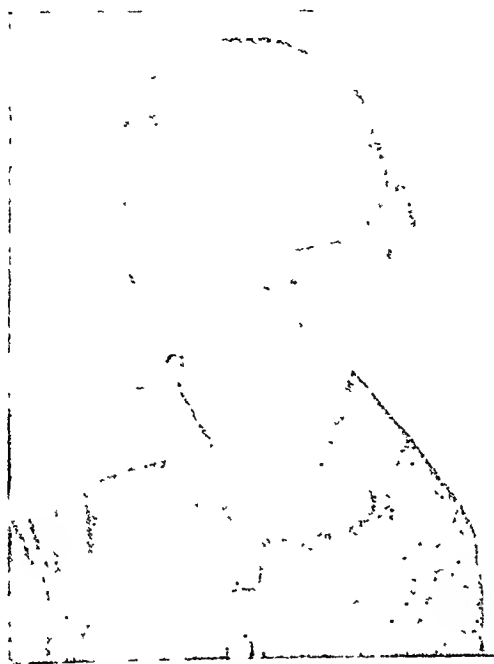


Fig. 4.—Case 2, before operation.

CASE 2.—Master E. H., 5-year-old white male, was admitted to the Touro Infirmary on June 1, 1938, with a diagnosis of parturitional torticollis. The patient's head was inclined toward the right, which was first noted two weeks after delivery. The child had been a breech presentation and was delivered by version and extraction with forceps on the aftercoming head. The deformity became more pronounced with time. The head was inclined toward the right at about a 30° angle. Extension and flexion of the head to the left were inhibited. The right half of the face was slightly smaller than the left; the scapulae were on an equal level. X-rays of the head and neck were negative for osseous deformity. The same operative procedure was performed as in Case 1 and again it was noted that some factor inhibited overcorrection. Again, further examination revealed a tense, hypertrophied scalenus anticus muscle, which, when sectioned, allowed liberal overcorrection. A body east was applied from the waistline to the forehead. After six weeks, the east was removed and a brace was applied and corrective exercises were instituted. In this case also an excellent result was obtained (Figs. 4 and 5).

CASE 3.—A. C., 15-year old white male, was admitted to the Touro Infirmary on Jan. 8, 1939, with a diagnosis of parturitional torticollis. Details of the patient's delivery were not available, but the deformity had been present since birth. The

as to whether or not the scalenus anticus is an etiologic factor, it is safe to sacrifice it, for in no case herein reported did one note any post-operative inhibition of head movements. The results obtained have been excellent, and although I have no right to base conclusions on such a small series, I do consider it of importance and worthy of attention in the future.

#### SUMMARY

1. A classification of torticollis is presented.
2. The term parturitional torticollis is more accurate than congenital torticollis.
3. Three cases of congenital torticollis are presented wherein the scalenus anticus muscle appears to have played a role in maintaining the deformity.
4. A discussion of the modus operandi of the scalenus anticus factor in congenital torticollis is presented.
5. It is suggested that definite examination of the scalenus anticus muscle be made at the time of operation in all cases of torticollis.

#### REFERENCES

1. Jones, R., and Lovett, R. W.: *Orthopedic Surgery*, New York, 1929, William Wood & Co.
2. Morris, Henry: *Human Anatomy*, Philadelphia, 1925, P. Blakiston's Son & Co.
3. Deaver, J. B.: *Surgical Anatomy*, Philadelphia, 1901, P. Blakiston's Son & Co., vol. II.

fourth, fifth, and sixth cervical vertebrae and is inserted into the tubercle on the inner border and under surface of the first rib in front of the groove for the subclavian artery. In parturitional torticollis in which there is fibrosis in the sternomastoid muscle and firm attachment of the muscle belly to its capsule, a shortening of the muscle occurs. Because of this, the head is depressed laterally toward the clavicle and first rib on the affected side. With the head in this position, the distance between the origin and attachment of the scalenus anticus muscle is likewise shortened. As the patient grows older and the scalenus anticus develops, it will be shortened in length but will be broader so it may appear hypertrophied. On the other hand there is also the



Fig. 6.



Fig. 7.

Fig. 6.—Case 3, anteroposterior view one year following operation

Fig. 7.—Case 3, head in hyperextension one year following operation.

possibility that the scalenus is hypertrophied because it also suffered a traumatic myositis at the time of delivery similar to that occurring in the sternomastoid. Although it cannot be considered as a primary etiological factor, it will act to maintain the deformity and can therefore be considered as a secondary etiological agent. If this chain of events is true, it is important that the scalenus anticus muscle be examined at operation in each case of torticollis. It is entirely plausible if the above hypothesis is accurate that the scalenus anticus factor may explain why sternomastoid myotomy is successful in some cases and fails in others.

However, a note of warning may be in order at this point. One should not indiscriminately sacrifice the muscles of the neck on the affected side for it is possible that the patient may be overcorrected and will then be more miserable than originally. If there is any doubt

The case histories of two patients treated at Grasslands Hospital are presented:

CASE 1.—This patient was a 4½-month old white male. On Nov. 30, 1938, while sitting in a baby carriage on the front porch of his home, he was bitten on the third and fourth fingers of his left hand by a rat. Merthiolate was applied immediately to the wounds without attempt at cauterization.



Fig. 1—Case 1 Rat-bite wound on the third and fourth left digits

On Dec. 6, 1938, the child was admitted to the surgical service because of inflammatory lesions on the fingers. At this time, the wounds appeared edematous, indurated, and dark bluish in color with all signs of inflammation. Direct smears and cultures of the lesions were negative for organisms. On admission the temperature was 100.2° but subsequently rose to 101.2°. It was relapsing in character with afebrile periods of four to five days. The Kline and Wassermann reactions were negative. The white blood count was 13,000. On the eighth hospital day the patient became lethargic, was nauseated, vomited, and had diarrhea. The red blood count was 2,900,000 as compared to 4,500,000 on admission. Treatment consisted of blood transfusions, parenteral fluids, and symptomatic therapy. On Dec. 9, 1938, blood cultures were taken and mice inoculated with venous blood. The *Spirilla morsus muris* were isolated on the twentieth day. Immediately, 0.2 Gm. of neoarsphenamine were given intravenously. This resulted in eradication of general symptoms, return of temperature to 98.8° within twenty four hours, and healing of the primary lesions within four days.

The patient was discharged on Dec. 21, 1938, as recovered. He has visited our follow up clinic periodically. On Jan. 10, 1939, the child was given another therapeutic injection of 0.2 Gm. of neoarsphenamine intravenously without untoward reaction. On Nov. 4, 1940, he was asymptomatic and had gained eleven pounds in weight. No scars were present at the site of the original lesions and function of the fingers was excellent. The Kline test was negative.

CASE 2.—This patient was a well developed, white 13 year old female admitted to the Pediatric Service and treated by that department. On Dec. 15, 1938, while playing at a garbage dump, she was bitten on the left wrist by a rat. It is interesting to comment that this girl lived in the same neighborhood as the infant of

## TWO CASES OF RAT-BITE FEVER

ALBERT G. ROGLIANO, M.D., VALHALLA, N. Y.

(From the Departments of Surgery and Pediatrics in Grasslands Hospital)

RAT-BITE fever was known in India as long as 2,300 years ago.<sup>1</sup> In 1839, Wilcox described a case seen in his practice which typified the course produced by the infection. Modern literature reveals that the disease is known in practically every country of the world. The main agency of spread is the bite of wild rats, but several cases have been attributed to the bite of cats,<sup>2</sup> squirrels, weasels, pigs, and monkeys. The disease is known as *sodoku*, from the Japanese "so," rat; and "doku," poison.

The exact etiology of rat-bite fever was discovered by Futaki and his associates in 1916. They called the organisms *Spirochaeta morsus muris*. It is a spirillum 3 by 4 U. long, approximately 0.2 U. thick, with pointed ends, carrying one or more flagella. The organism has a very rapid darting, to-and-fro motion, with a spinning movement around the long axis. It has never been cultivated in artificial media. The organism can be identified by Giemsa or Wright stain and dark-field examination. The material should be obtained from venous blood and cultured by mouse inoculation. The procedure is as follows: Two cubic centimeters of blood from an infected patient is injected into the peritoneal cavity of a mouse. An incubation period of from fourteen to twenty days is allowed to elapse. At the end of this time, the cardiac blood of the mouse is examined for the organisms.

In pathogenicity the *Spirillum morsus muris* bears a resemblance to *Spirochaeta pallida* and like it is destroyed by arsenical drugs. Where the skin is perforated by the rat bite, usually on the hands, arms, or lower extremities, a lesion develops presenting the gross appearance of a granuloma without evidence of suppuration.<sup>3</sup> The tissue sections of the wound at the point of entrance, when examined under the microscope, reveal necrosis of the epithelium and dense round-cell infiltration of the corium. The parenchymatous organs present a generalized picture of toxemia as might be expected from a continued intermittent febrile disease. Hyperplastic dilated sinuses and hyperemia of the suprarenal glands and of the cortex of the spleen are also found. The central arteries of the malpighian bodies in the spleen develop hyaline degeneration.

The significant laboratory findings were leucocytosis of 13,000; hemoglobin, 12 Gm.; and red blood cells, 4,690,000. On admission the Kline test was doubtful, but twenty-four days later it became positive. During the temperature peak the examination of the venous blood on direct smear revealed *Spirilla morsus muris*. This was confirmed by mouse inoculation.

On Feb. 2, 1939, 0.3 Gm. of neoarsphenamine was administered intravenously. The child immediately became asymptomatic and afebrile. On Feb. 10, 1939, 0.3 Gm. of neoarsphenamine was again given intravenously. She was discharged on Feb. 18, 1939, as recovered. When seen in the follow-up clinic she had gained weight and had been asymptomatic since discharge. Primary lesions had caused no scars. The last visit was on Nov. 8, 1940, at which time the Kline test was still positive.

#### SUMMARY

Rat-bite fever is a rare disease in the United States. These were the first cases seen at Grasslands Hospital, and only 91 cases have been reported in the American literature. Nevertheless, it is a disease which may be diagnosed without unusual difficulty and may be successfully treated. The Kline test is positive in 50 to 60 per cent of cases during the acute phase of the infection but will eventually become negative.<sup>4</sup>

The clinical course<sup>5</sup> is characterized by development of an inflammatory lesion at the site of injury followed by the onset of fever with recurrent paroxysms of chills and fever, muscular aches and pains, cutaneous eruption, lymphadenitis and lymphangitis, neutrophilic leucocytosis, and varying degrees of prostration, and responds promptly to the administration of arsphenamine (and similar drugs) intravenously.

#### REFERENCES

1. Jones, Bayne: Rat Bite Fever in United States, *Internat. Clin.* 3: 235-253, 1931; *Arch. Ophth.* 4: 858-869, 1932.
2. Laverick, J. V.: Rat-bite Fever From Cat, *Brit. M. J.* 1: 639-640, 1936.
3. MacDermott, E. N.: Rat Bite Fever—A Study of the Experimental Disease, With a Critical Review of the Literature, *Quart. J. Med.* 21: 433-458, 1927-28.
4. Edelman, S. D., and Haber, G. B.: Rat-bite Fever; Report of Three Cases With Review of Literature, *J. Pediat.* 5: 520-530, 1934.
5. Leadingham, R. S.: Rat Bite Fever, Report of Five Cases, *Am. J. Clin. Path.* 8: 333-344, 1938; abstracted in *J. A. M. A.* 89: 239, 1927.



Case 1. The emergency treatment consisted of cauterization and tetanus antitoxin. Two days later, local signs of inflammation with lymphadenitis appeared. These subsided in forty eight hours. The patient remained asymptomatic until the seventh day when she became nauseated, vomited, and suffered from headache, malaise,



Fig. 2.—*Spirilla morsus muris* isolated from mouse inoculation (from blood of patient in Case 2)

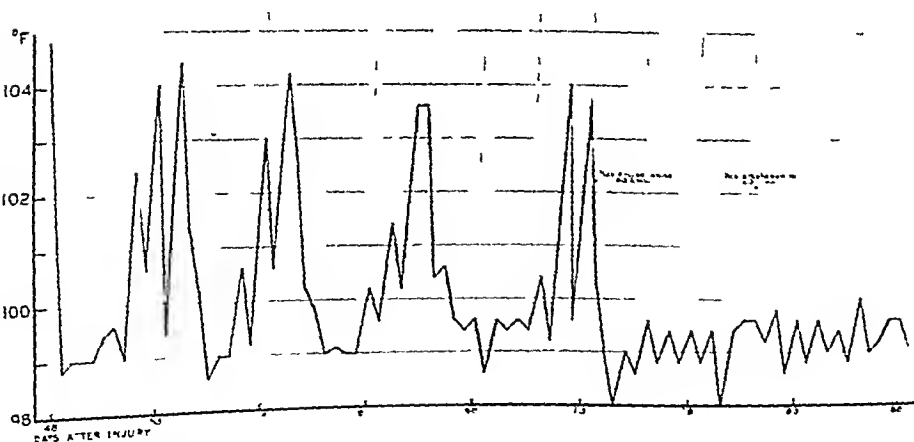


Fig. 3.—Temperature course of patient in Case 2. Injections of neorsphenamine indicated on chart.

lethargy, and generalized muscular pains. At this time she was admitted to the hospital. Paroxysms of chills and fever recurred at five day intervals. On the thirty second day a maculoerythematous rash appeared.

The significant laboratory findings were leucocytosis of 13,000; hemoglobin, 12 Gm.; and red blood cells, 4,690,000. On admission the Kline test was doubtful, but twenty-four days later it became positive. During the temperature peak the examination of the venous blood on direct smear revealed *Spirilla morsus muris*. This was confirmed by mouse inoculation.

On Feb. 2, 1939, 0.3 Gm. of neoarsphenamine was administered intravenously. The child immediately became asymptomatic and afebrile. On Feb. 10, 1939, 0.3 Gm. of neoarsphenamine was again given intravenously. She was discharged on Feb. 18, 1939, as recovered. When seen in the follow-up clinic she had gained weight and had been asymptomatic since discharge. Primary lesions had caused no scars. The last visit was on Nov. 8, 1940, at which time the Kline test was still positive.

#### SUMMARY

Rat-bite fever is a rare disease in the United States. These were the first cases seen at Grasslands Hospital, and only 91 cases have been reported in the American literature. Nevertheless, it is a disease which may be diagnosed without unusual difficulty and may be successfully treated. The Kline test is positive in 50 to 60 per cent of cases during the acute phase of the infection but will eventually become negative.<sup>4</sup>

The clinical course<sup>5</sup> is characterized by development of an inflammatory lesion at the site of injury followed by the onset of fever with recurrent paroxysms of chills and fever, muscular aches and pains, cutaneous eruption, lymphadenitis and lymphangitis, neutrophilic leucocytosis, and varying degrees of prostration, and responds promptly to the administration of arsphenamine (and similar drugs) intravenously.

#### REFERENCES

1. Jones, Bayne: Rat Bite Fever in United States, *Internat. Clin.* 3: 235-253, 1931; *Arch. Ophth.* 4: 858-869, 1932.
2. Laverick, J. V.: Rat-bite Fever From Cat, *Brit. M. J.* 1: 639-640, 1936.
3. MacDermott, E. N.: Rat Bite Fever—A Study of the Experimental Disease, With a Critical Review of the Literature, *Quart. J. Med.* 21: 432-458, 1927-28.
4. Edelman, S. D., and Haber, G. B.: Rat-bite Fever; Report of Three Cases With Review of Literature, *J. Pediat.* 5: 520-530, 1934.
5. Leadingham, R. S.: Rat Bite Fever, Report of Five Cases, *Am. J. Clin. Path.* 8: 333-344, 1938; abstracted in *J. A. M. A.* 89: 239, 1927.

## INTESTINAL OBSTRUCTION AS A PHASE OF CARCINOMA OF THE CERVIX\*

BJARNE PEARSON, M.D., AND MANUEL GARCIA, M.D., NEW ORLEANS, LA.  
(From the Departments of Pathology and Bacteriology and of Radiology of the  
School of Medicine of Louisiana State University and Charity Hospital  
of Louisiana at New Orleans)

NEOPLASTIC obstruction of the intestine, though long recognized, is an apparently neglected phase of cervical carcinoma. Incidental allusions to this feature of the disease are found in the literature, but factual elaboration of the subject has seldom been attempted. Only a minority of cases suitable for operative relief reach the surgeon, and the significance of incipient low-grade obstruction seems to be generally overlooked. The present communication offers relevant information obtained from a review of autopsy material at Charity Hospital of Louisiana at New Orleans.

During the eleven-year period ending Jan. 1, 1941, 74 cases of squamous-cell carcinoma of the cervix came to necropsy in this institution. Adenocarcinomas are excluded from this study. In 9 of these cases a diagnosis of intestinal obstruction had been entertained clinically, or had actually been confirmed, and post-mortem examination in each instance disclosed neoplastic extension to the bowel with definite reduction of its caliber. The incidence of intestinal obstruction in the autopsied material of cervical carcinoma is thus 12.1 per cent, which agrees with the figures previously reported by one of us (B. P.) in a similar series.

In these 9 cases three portions of the bowel showed neoplastic involvement which eventuated in obstruction: The ileum was affected in 3, the sigmoid in 1, and the rectum in 5. A double obstruction was present in 3 cases. The pathogenesis and mechanism of obstruction were of several types (Table I), but in all instances the degree of constriction was severe, since the study included only those with symptoms of obstruction.

In only 1 case (Case 8) was the obstruction complete. In this instance an annular metastasis to the ileum was located 20 cm. from the ileocecal valve and was so bulky that it was palpable through the abdominal wall in the right lower quadrant. A second ileal lesion (Case 5) occurred in a dependent loop of bowel attached to a tumor mass in the cul-de-sac of Douglas. Marked stenosis of the ileum resulting from the cancerous infiltration and fecal impaction produced functionally complete obstruction terminating in perforation of the gut and peritonitis. The third ileal lesion (Case 7) was identical except that rupture took place into the vagina and an ileovaginal fistula was thus created.

In Case 6 a serosal implant had penetrated through the wall of the sigmoid, and after fungating internally had caused marked attenuation of the lumen. In Case 9 the ampullary portion of the rectum was functionally obliterated by pressure of a large carcinomatous mass growing diffusely in the pelvis. In Case 3 the same area was narrowed to a diameter of 2 cm. by intramural proliferation of an invading neoplasm.

TABLE I

TYPES OF INTESTINAL OBSTRUCTION IN CARCINOMA OF THE CERVIX

PATHOGENESIS	ROUTE OF DISSEMINATION	MECHANISM	EXAMPLE
Spread in the pelvis (I)	Infiltration of contiguous structures	1. Encirclement of the rectum 2. Compression of the rectum by a large pelvic tumor 3. Fungation of neoplasm into rectal lumen	Cases 1, 3, and 4 Case 9 Case 2
	Invasion of peritoneum	4. Stenosis of dependent loop of ileum	Cases 5 and 7
	Peritoneal seeding	5. Bulky growth of serosal implants on the sigmoid	Case 6
Metastases (II)	Blood stream	6. Isolated metastasis to small intestine producing constriction	Case 8
	Lymphatics	7. Infarction of bowel due to pressure on vessels by large mesenteric nodes	Case A35-359

In 3 other rectal strictures (Cases 1, 2, and 4), in which the residual lumen varied from 1 to 1.5 cm. in diameter, the principal area of involvement was characteristically at the level of the portio. In all 3 cases the lower edge of the constriction had been palpable clinically 5, 8, and 10 cm. respectively from the anus. Carcinomatous infiltration in the reetovaginal septum and the uterosacral ligaments completely encircled the rectum, involving the muscularis but not the mucosa. Rectal strictures of this type were also present in Cases 5 and 7 in addition to the ileal stenosis already described. In Case 9 obstruction at the same site (rectum) had been produced at different times by two distinct etiologic agents. The pressure of a pelvic abscess secondary to infection in the cervical growth had first rendered the rectum essentially impervious, and ten months later (three months before death) the rectum was again found blocked, this time by an extrinsic tumor.

A type of obstructive infarction which did not occur in the series of cases reported in this paper is illustrated by the following case history:

S. S. (A35-359), a colored woman, 65 years of age, was seen in August, 1934, with a mass in the cervix. The uterus was curetted and adenocarcinoma was found, which was treated by both radium and x-ray therapy. In February, 1935, a subcutaneous metastasis in the thigh was excised and clearly exhibited the structure of squamous carcinoma. The patient died a month later. Seeding of the peritoneum was found at autopsy; mesenteric nodes had produced compression and thrombosis of the mesenteric vessels with infarction and perforation of the small intestine.

TABLE II  
CARCINOMA OF THE CERVIX WITH INTESTINAL OBSTRUCTION

NO.	COLOR AGE STAGE FIRST ADMIS- SION	PERIOD OF OB- SERVA- TION PRIOR TO OB- STRUC- TION	SYMPTOMS OF OBSTRUCTION	MEASURES FOR RELIEF OF OBSTRUCTION	LOCATION AND MECHANISM OF OBSTRUCTION	SUR- VIVAL AFTER OBSTRUC- TION	MAIN CAUSES OF DEATH	EXTENT OF TUMOR INVOLVEMENT
1	W 53 IV	None	Progressive, severe, in- termittent, crampy, colicky pains with vom- iting and abdominal dis- tention of 2 wk. dura- tion	Rectal tube; sigmoid colostomy	Rectum stricture 10 cm. from anus	Post- opera- tive death	Intestinal obstruction	Diffuse invasion of pel- vis and peritoneal dis- semination
2	C 25 II	6 mo.	Abdominal pain, disten- tion and severe dysche- sia	Conservative	Rectum stricture 5 cm. from anus	5 mo.	Uremia	Diffuse infiltration of pelvis and bladder
3	C 54 IV	None	Abdominal distention, vomiting, loss of weight, anorexia and intermit- tent abdominal pain of 3 wk. duration	Repeated enemas; sigmoid colostomy	Rectum mass 5 cm. from anus	5 days	Intestinal ob- struction; postoperative peritonitis	Tumor in rectum and parametria
4	C 36 II	8 mo.	Abdominal pain, generalized	Conservative	Rectum stricture 8 cm. from anus	3 wk.	Endometritis, sepsis	Perirectal, vaginal, uterine involvement; pelvic and retroperi- toneal nodes

		10 mo.	Severe constipation and vomiting for 1 wk; abdominal distention, no bowel movements for 5 days	Conservative	Rectum stricture; lower ileal stenosis	6 wk.	Intestinal obstruction, ileal perforation and peritonitis	Diffuse infiltration of pelvis, peritoneal dissemination, metastasis to umbilicus and pelvic nodes
5	W 55 III							
6	W 52 IV	None	Lower abdominal pain for 6 months; intermittent colicky abdominal pain, nausea, vomiting, and anorexia and abdominal distention for 3 mo	Conservative	Sigmoid adhered to uterus; nodule protruding 2 cm. into lumen	7 mo.	Carcinomatosis	Tumor in sigmoid, uterus, vagina, bladder, peritoneum, liver, stomach, lungs, pericardium
7	W 58 III	16 mo.	Abdominal pain; pain in rectum and diarrhea for a few days	Conservative	Rectum stricture; mass encircling rectum 6 cm. from anus; stenosis of ileum	2 mo.	Intestinal obstruction, peritonitis	Periureteral, bladder, and ileal involvement
8	C 69 IV	None	Colicky pains in the abdomen with nausea and vomiting of 3 mo. duration	Resection of ileum	Occlusion of ileum 20 cm. above cecum	2 wk.	Intestinal obstruction, peritonitis	Tumor in ileum, uterus, tubes and ovaries; metastasis to liver
9	W 10 III	None	First admission; crampy abdominal pain, nausea and vomiting	Colpotomy; 250 c.c. of pus drained	Rectum, extrinsic pressure by pelvic abscess	3 mo.	Uremia, anemia, sepsis	Periureteral, bladder, and vaginal involvement; peritoneal dissemination; pelvic and iliac nodes
		10 mo.	Second admission; progressive rectal pain, marked dysesthesia	Conservative	Rectum, extrinsic compression by tumor			

In 3 of the 74 cases of carcinoma of the cervix which form the material for this study large mesenteric nodes were observed, and peritoneal seeding was found in 10 other cases. On this basis, one is justified in assuming that obstructive infarction might also be produced by a pure squamous-cell carcinoma.

Another type of obstruction is described by Lacassagne. The actual occurrence of the mechanism is not definitely established, however, since the cases which he reported were not controlled by autopsy. In 2 of 7 cases in which massive prevertebral lumbar nodes were observed after permanent healing of the pelvic lesions, the intestine was "compressed" and symptoms of obstruction were present. Retroperitoneal metastases were observed in 9 of the 74 cases which we studied, but either the nodes were not bulky enough to impinge on the bowel or their location was not such as to produce obstruction. These observations suggest that as control of the lesions in the pelvis by radiation becomes more general, this mechanism of intestinal obstruction is likely to become of more clinical importance.

A résumé of the clinical and pathologic characteristics exhibited in this series (Table II) shows that the cases fall into two groups. In 5 cases obstructive symptoms dominated the picture, the patients applying to obtain relief from the intestinal condition rather than for treatment of the neoplasm. The other 4 patients had been treated for carcinoma of the cervix and obstruction developed later, while they were being followed up. The 5 patients in the first group complained of intermittent colicky abdominal pain associated with nausea, vomiting, and abdominal distention. The disturbances had been present for one to three weeks in the patients with rectal lesions (Cases 1, 3, and 9), and at intervals for three months in the patients with obstruction of the ileum (Case 8) and of the sigmoid (Case 6). In these cases the symptoms had been mild and intermittent in the beginning but had become much worse just prior to the patients' admission to the hospital.

In all 5 cases the manifestations of intestinal obstruction were so typical that the diagnosis was made clinically. Sigmoid colostomy was performed in Cases 1 and 3, and resection of the ileum in Case 8. All 3 patients died shortly after operation. In Case 9 drainage of a pelvic abscess by colpotomy brought relief for ten months, and in Case 6 the patient survived seven months under conservative treatment.

In the other 4 cases the patients had been under observation for periods varying from six to sixteen months prior to the onset of obstruction. Rectal constriction was present in all the patients in this group, and Case 9 might also be included in it, since this patient had been under observation for ten months when her second constriction developed. In addition to the rectal involvement, ileal stenosis was also present in Cases 5 and 7. The symptoms complained of by all the patients in this group were milder and progressed more slowly than in the

first group. Distention, constipation, dyschesia, and abdominal pain were always present, but were so vague and inconstant and so obscured by other manifestations of the disease that the gravity of the obstruction was not recognized and no effective treatment was instituted.

In 2 instances (Cases 2 and 9) the cause of death was uremia. One patient died of sepsis (Case 4) and another of generalized carcinomatosis (Case 6). The remaining patients died of intestinal obstruction, which thus was the immediate cause of death in 6.7 per cent of the 74 patients who came to autopsy.

#### COMMENT

An extensive search of the British and American literature has revealed no titles directly concerned with the tendency of carcinoma of the cervix to cause intestinal obstruction. Ewing mentions infiltrative compression of the rectum and Healy states that colostomy is sometimes required to relieve obstruction. Brief reference to the subject is made by Cutler and Buschke, Cade, Warren, and Stout. Healy and Frazell, in 626 clinical cases of carcinoma of the cervix, found 9 rectal strictures, 3 of which required "operative interference." Maliphant, in a study of 500 cases, found 8 instances of intestinal obstruction due to carcinomatous stricture. Gal, in a clinical survey of 2,320 cases, found carcinomatous involvement of the rectal mucosa in 13 patients, but does not mention obstructive lesions.

Halter seems to be the only author who has attempted a comprehensive study of the subject. In an analysis of 453 inoperable cases of carcinoma of the cervix he found anatomic changes in the lower portion of the intestine in 87 cases (19.2 per cent). In our series of 74 cases, which can fairly be considered analogous, the incidence of rectal involvement was 21.6 per cent, a reasonably close agreement. In 11 of Halter's cases obstructive symptoms figured prominently in the clinical picture. He considers obstruction to be an important factor in the development of fistulas and stresses encirclement of the rectum opposite the level of the portio. We have already commented upon this type of involvement.

In an earlier study of 57 consecutive autopsied cases of carcinoma of the cervix one of us (B. P.) found 14 instances of rectal involvement, exclusive of fistulas. Stricture was present in 7 cases, in 3 of which colostomy was required, and death resulted from unrelieved intestinal obstruction in another case in this group.

The therapeutic measures ordinarily instituted for intestinal obstruction are applicable in the cases in which it develops from carcinoma of the cervix. Decompression of the colon by tidal irrigation, as advocated by Wangensteen, is useful, and Treves states that symptoms of low-grade obstruction in advanced cases of cervical carcinoma can be controlled by mild purgation and careful attention to diet. Colostomy,



however, seems to be an inescapable step in most cases, and can contribute greatly both to the patient's comfort and to prolongation of life if it is not delayed too long. It has been performed with increasing frequency and with gratifying results on our service in the New Orleans Charity Hospital during the past year, and a deliberate effort is now being made to discover incipient obstructive lesions. The value of the operation is well illustrated in the following cases, which are not included in this series because they did not come to autopsy:

Mrs. S. D. (III-40892), a white female, 42 years of age, was treated with radium and x-ray in April, 1933, for squamous-cell carcinoma of the cervix. In October, 1933, she developed obstipation which lasted for nine days. Exploratory laparotomy showed the uterus to be adherent to the left pelvic wall, and annular constriction of the sigmoid caused by tumor extensions. Colostomy was performed. The patient remained symptom-free until May, 1935, when reactivation of the growth apparently occurred. She died in July, 1935, nineteen months after operation.

C. R. (III-69541), a colored female, 48 years of age, had had a supravaginal hysterectomy for uterine leiomyoma in 1920. She entered the hospital in April, 1936, with transitional-cell carcinoma of the cervical stump, for which she was treated with x-ray (1,500 r.  $\times$  4 over the pelvis), followed by the interstitial application of radium (2,400 mg. hr.). In April, 1937, she developed an obstruction of the rectum due to carcinomatous stricture, for which colostomy was done. She remained well until July, 1938, when a vaginointestinal fistula appeared. Roentgenologic study of the gastrointestinal tract showed a communication between the ileum and the vagina. The lesion was thought to be a radiation injury and no surgery was attempted. Although the patient was alive in December, 1939, she was too ill to make the trip to the hospital and she died shortly afterward. The known period of survival after colostomy was thirty-two months.

It is worth pointing out that rectal involvement does not necessarily mean that the patient's condition is hopeless. Gal treated several of his patients with carcinoma of the cervix with extension to the rectum by the implantation of radium, and 2 were known to be alive and well ten years and thirteen years later.

#### SUMMARY AND CONCLUSIONS

In 74 squamous-cell carcinomas of the cervix which came to necropsy at Charity Hospital of Louisiana at New Orleans over an eleven-year period the incidence of carcinomatous obstruction of the bowel was 12.1 per cent. Intestinal obstruction was the immediate cause of death in 6.7 per cent of this series. The case records and the types of obstruction are discussed. In 5 cases the intestinal obstruction initiated the clinical picture. Obstruction also develops insidiously in treated cases, with symptoms so obscure that alertness is required for its recognition. Colostomy is an effective palliative measure and rectal involvement deserves vigorous treatment, for an occasional so-called cure may be obtained. A plea is made for early detection and prompt, adequate treatment of obstructive intestinal lesions arising from carcinoma of the cervix, to effect better palliation and secure longer survival.

## REFERENCES

1. Cade, Stanford: *Malignant Disease and Its Treatment by Radium*, Baltimore, 1940, Williams and Wilkins Co., p. 847.
2. Cutler, M., and Buschke, F.: *Cancer: Its Diagnosis and Treatment*, Philadelphia, 1938, W. B. Saunders Co., p. 355.
3. Ewing, James: *Neoplastic Diseases*, ed. 4, Philadelphia, 1940, W. B. Saunders Co., p. 619.
4. Gal, Felix: Ueber Mastdarmkomplikationen bei Gebärmutterkrebskranken, *Strahlentherapie* 64: 125-133, 1939.
5. Gal, Felix: Rectal Complications of Uterine Cancer; Differential Diagnosis of Cancer Metastasis and Radiation Proctitis, *Magyar röntgen Kéz.* 12: 78-83, 1938.
6. Halter, Gustav: Anatomische und functionelle Veränderungen des Rectums beim Collumcarcinom, *Arch. f. Gynäk.* 151: 126-149, 1932.
7. Healy, W. P.: Cancer of Uterus and Its Treatment by Irradiation, *Am. J. Obst. & Gynec.* 10: 789-798, 1925.
8. Healy, W. P., and Frazell, E. L.: Methods and Results of Treatment in Carcinoma of the Cervix at Memorial Hospital, *Am. J. Obst. & Gynec.* 34: 593-606, 1937.
9. Lacassagne, Antoine: Les métastases des épithéliomas du col utérin localement guéris par radiothérapie, *Ann. Surg.* 93: 460-466, 1931.
10. Maliphant, Glynn R.: Complications of Radium Therapy in Cancer of the Uterine Cervix, *J. Obst. & Gynaec. Brit. Emp.* 46: 873-884, 1939.
11. Pearson, Bjarné: Causes of Death in Carcinoma of the Cervix, *Am. J. Cancer* 28: 31-39, 1936.
12. Stout, Arthur P.: *Human Cancer*, Philadelphia, 1932, Lea and Febiger, p. 358.
13. Treves, Norman H.: In Pack and Livingston: *Treatment of Cancer and Allied Diseases*, New York, 1940, Paul B. Hoeber, Inc., vol. III, p. 2568.
14. Wangensteen, Owen: In Christopher Frederick: *Textbook of Surgery*, ed. 2, Philadelphia, 1939, W. B. Saunders Co., p. 1138.
15. Warren, Shields: Studies on Tumor Metastasis; Distribution of Metastases in Carcinoma of the Cervix Uteri, *Surg., Gynec. & Obst.* 56: 742-745, 1933.

# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## RECENT ADVANCES IN THE SURGICAL TREATMENT OF CARCINOMA OF THE COLON AND RECTUM

RICHARD B. CATTELL, M.D., AND EVERETT D. SUGARBAKER, M.D.,  
BOSTON, MASS.

*(From the Department of Surgery of the Lahey Clinic)*

SINCE it is our purpose to discuss recent advances which have taken place in the surgical treatment of cancer of the large bowel, it seems fitting that attention should first be directed to information obtained from the fields of radiology and pathology to which surgery must remain indebted for a clearer definition of the problem involved.

### RADIATION THERAPY

Radiation therapy for these lesions has had an extensive trial. With the accessibility of rectal cancer, interstitial radon application was a natural development. Likewise, radiation therapy alone or in conjunction with radium was extensively used. A sufficient amount of clinical data based on the use of modern equipment and methods is now available to justify several conclusions.

Foremost is the now well-established fact that in general these cancers are markedly radioresistant.<sup>26</sup> Unfortunately the surrounding tissues frequently display little, if any, greater resistance than do the neoplasms to which they give rise, with the result that dosages calculated to destroy the growth almost invariably produce extensive necrosis and at times sepsis. It seems reasonable to conclude further, by analogy with cancers of the breast, oral cavity, and so forth, that secondary deposits in the regional nodes are probably even less affected by this form of treatment than are the primary tumors themselves. Since it is not possible to determine by clinical means when and to what extent these metastases are present, the benefits to be derived from irradiation alone become still less certain.

Despite these unfavorable circumstances, as high as 50 per cent five-year survivals following these methods have been reported among a small selected group of rectal carcinomas.<sup>3</sup> As might be expected, however, even this figure does not compare well with the five-year results of radical surgery which in a favorable selected group exceed 90 per cent. Occasional apparent cures of patients said to have inoperable lesions when diagnosis was made are also reported, though the particular criteria establishing inoperability are usually not cited.<sup>27</sup>

Finally, there is general agreement that a certain amount of palliation may frequently, though not invariably, be obtained as evidenced by diminution of symptoms and prolongation of life.<sup>2 24</sup> It therefore seems reasonable to state that irradiation should be strictly reserved as a primary form of treatment for cases that prove technically inoperable, which in our experience represents but 15 per cent of our cases.

#### PATHOLOGY

Further definition of the problem has been presented by the painstaking work of Westhues,<sup>30</sup> Gabriel, Dukes, and Bussey,<sup>9</sup> and by Gilchrist and David.<sup>10</sup> Careful examination by them of accumulating surgical material has shown the incidence of node metastasis in rectal carcinomas to be in the neighborhood of 60 to 70 per cent. This is about twice as high as had previously been realized. It is probable that similar care in the examination of colon specimens would be equally surprising.

A consideration of these facts clearly delineates the problem and indicates both the type and extent of treatment necessary to meet it. By present day methods a reasonable chance of cure may obviously be obtained only by wide resection of the primary tumor accompanied by as complete a regional node removal as is anatomically possible. To accomplish this, adjacent invaded organs, such as a segment of small intestine or ureter, a portion of the urinary bladder, the uterus and its adnexa, or portions of the vaginal wall or prostate must frequently be removed en bloc with the tumor. When in rectal tumors there is extensive involvement of the inferior mesenteric node chain, the inferior mesenteric artery may be ligated at the point where it leaves the aorta in the expectation of remaining above the diseased nodes.

#### OPERATIVE MANAGEMENT

Such increasing radicalness of thought is reflected in a steadily rising operability rate which began at the Lahey Clinic at 58.3 per cent in 1929 and has risen to 84 per cent during the past two years. The figures of others have indicated a similar trend.<sup>1 13 14 22</sup> In addition, the incidence of abdominoperineal rectal resections performed has risen to 85 per cent, the less radical posterior resection and the anterior resection being employed in a diminishing number of instances.

One of the chief factors making this possible has been the two-stage rectal resection first described by Lahey<sup>16</sup> in 1930, and since somewhat modified.<sup>15</sup> This plan of procedure has permitted the acceptance for resection of many aged patients with degenerative circulatory changes which leave them on the verge of cerebral accidents, cardiac failure, and anemia. Actually, 9 per cent of patients on whom resection is performed at the clinic are between seventy and eighty years of age. When perforation of the tumor with abscess formation has occurred, drainage may be instituted at the first stage, thereby permitting a

much easier subsequent removal of the tumor without the risk of spreading infection. Many patients in whom extension of the growth to contiguous organs or structures has taken place, and who for other reasons are poor risks, have proved safely resectable by this means whereas the hazards of a Miles operation would almost certainly have been too great. In 16 per cent of instances it has been necessary to remove either partially or entirely some adjacent organ or other structures.

In general, then, the two-stage operation has permitted more of the usual radical resections in poor risk patients and a greater number of the more extensive procedures in the good and average risk groups. This is true because rectal resection done as a second stage procedure is physiologically less disturbing than when carried out in one stage. There are several good reasons for this: (1) A well-functioning colostomy is already present; (2) careful exploration of the abdomen and division of the bowel have already been done at the first stage, thereby confining the second stage entirely to the pelvis; (3) coincident infection can be more adequately cared for either by actual drainage at the first stage (if perforation has occurred) or by irrigation of the tumor segment between stages; and (4) the resection may be done in less time for not only has the colostomy been already prepared but the surgeon now knows exactly what must be done even before the abdomen is opened. In recognition of these advantages the two-stage operation is now carried out in about one-half of all resected cases.

From time to time various objections to this procedure have been raised: (1) The opportunities for the development of those complications which may follow any operation are doubled, (2) the abdomen is entered the second time through a potentially infected field, (3) adhesions resulting from the first stage may make the second stage more difficult than a Miles resection, and (4) the lapse of two weeks provides additional time for metastases to occur. The first of these objections is a valid one but is more than compensated for by the increased operability permitted and by the proportionately better individual chances for cure offered because more patients are treated by the abdominoperineal method and fewer by the less radical posterior resection. The second objection is sound in theory only. In actual practice, wound infections are rarely seen after the second stage operation and peritonitis has been largely eliminated as a cause of postoperative death. In answer to the third argument, it may be stated that if the first stage has been properly done troublesome adhesions rarely will be found at the second stage. Regarding the possibility of metastases occurring during the fourteen-day interval between stages, it may be said that this factor must be small indeed when one considers that the average duration of symptoms from onset to application for treatment is from nine to twelve months. It is of little value to mention operability figures without discussing at the same time operative mortality and end results.

When approximately nine of every ten patients seen are being operated on, it becomes obvious that the hazards in some are unavoidably high. During the same period (1929-1939) previously mentioned, during which the operability steadily rose, the operative mortality dropped from 36 per cent to 12.4 per cent. There is little doubt that if all patients could be operated upon during the time when their lesion is still confined to the bowel wall—and this is unfortunately true of less than one-third of the total number—the immediate mortality could probably be kept in the neighborhood of 5 per cent.

If a reasonable operative mortality in surgery of the large bowel is to be maintained, strict attention to three important factors is essential:

1. Adequate preoperative preparation.
2. A carefully planned system of operative procedure in which untoward eventualities are anticipated.
3. Institution of certain measures designed to reduce or eliminate postoperative complications.

It is not possible to lay down any rule as to how long a preoperative period of preparation is necessary. There are a few very good-risk patients with small lesions for whom three days would suffice. At the other extremity are those dangerous-risk patients who present, in addition, advanced lesions which forecast difficult surgery. Preparing such patients will require more time and much thought. A safe formula would be to allow as long as is necessary for an optimal re-establishment of function both local and systemic. When a two-stage operation is decided upon preoperatively, a short period should suffice.

The necessity for thorough decompression of the gastrointestinal tract, especially when some degree of obstruction is present, is now generally appreciated. Measures undertaken to fortify lowered cardiorenal reserve, and to replace deficient fluid, salts, and blood, it must be remembered, are no less important. It is doubtful if there is anything to be gained by the preoperative administration of vitamin concentrates unless there is good reason to believe that previous intake has been inadequate.

There are probably no two surgeons whose operative management of these cases is identical and it is in many respects true that for each his way is best. However, because of the frequently unsuspected situations which can arise during large bowel surgery, certain measures are routinely incorporated in all of these procedures because of the added safety which they contribute.

Most important among these is spinal anesthesia. The complete muscular relaxation which it affords permits easy exposure of the operative site, makes the frequent rehandling of the small intestine unnecessary, and allows unhampered wound closure. These advantages can only be fully appreciated when such unforeseen misfortunes as the inadvertent entering of an abscess cavity, or troublesome bleeding deep in the pelvis,

are superimposed on an already difficult problem. Either pontocaine-glucose<sup>20</sup> or nupereaine<sup>12</sup> is used.

It has also become a routine policy to have an intravenous infusion of normal saline solution running before operation is begun. Its purpose is to provide the anesthetist with a quick and easy means of responding to variations in the patient's general condition by the prompt administration of appropriate intravenous medications or blood. Prolonged drops in blood pressure as well as other less serious incidents are thereby prevented. Usually an ankle vein is selected because the necessary manipulation can be carried out here without interfering with the progress of the operating team.

Since it is rarely possible to predetermine exactly what type of procedure shall be suited to the peculiar exigencies of each case, the type of incision employed is important. This is particularly true for lesions distal to the midpoint of the transverse colon. The ideal incision should permit easy exposure for the carrying out of whatever type of operation seems necessary and should also, in healing, leave a solid abdominal wall. We believe that an incision through the outer third of the left rectus muscle fulfills both of these qualifications. It allows easy exploration of all of the abdominal viscera and may easily be extended either upward or downward for sigmoid or transverse colostomy (either of the loop or Mikuliez types) or for one- or two-stage abdominoperineal resection of the rectum. When freeing of the splenic flexure is necessary, this may be somewhat more easily accomplished here than through a midline incision. It is possible that this incision results in a somewhat higher incidence of weakness of the abdominal wall or even hernia, but in our opinion, the ease of carrying out the difficult operative procedure more than compensates for this possible disadvantage.

Among the postoperative complications of large bowel surgery, shock and peritonitis have in the past occupied the positions of primary importance. Serious grades of the former have now been satisfactorily disposed of by routinely transfusing either during or immediately following operation. Peritonitis has been largely eliminated by the employment of the exteriorization resection (modified Mikuliez) type of procedure for all colon lesions except those low in the sigmoid. In tumors of the right colon such an operation has its greatest usefulness, for the relative thinness of this side of the bowel as compared to the more distal portions, as well as the higher degree of infectiveness of its contents makes anastomosis in this region especially hazardous. The technique followed in Mikuliez resections of the right colon is that described by Dr. Lahey<sup>17</sup> in 1931. In view of the recent trend in the treatment of carcinoma of the right colon away from one-stage resection toward anastomosis followed by resection at a second stage,<sup>1, 21</sup> the Mikuliez operation may be said to have still another recommendation, namely that it involves but a single entering of the peritoneal cavity, the subsequent colostomy closure being accomplished entirely outside the peritoneal cavity.

Postoperative urinary complications are seen primarily following removal of the rectum and occur in about 75 per cent of these cases. Ewert<sup>7</sup> has recently reported the experience at this clinic in the management of these complications. They are rarely fatal but may be extremely troublesome and usually result from injury to the pelvic parasympathetic nerves (*nervi erigentes*) arising from sacral segments two, three and four. Stretching or severing of these fibers produces diminution in bladder tone, the degree and duration of which is proportionate to the extent of injury. Resection of large infiltrating tumors of the upper rectum and rectosigmoid is most apt to cause bladder atony.<sup>25</sup> To prevent urinary stasis, further loss in muscle tone, and ensuing infection, it is useful to employ constant closed bladder drainage by means of an indwelling catheter for seven to ten days postoperatively. Occasionally slightly longer periods are necessary. In males moderate degrees of prostatic obstruction previously unnoticed may become evident because of weakened detrusor action, and are relieved by transurethral resection.<sup>7</sup>

#### END RESULTS

To quote end results it is necessary to present cases of patients operated upon five years or more ago.<sup>4</sup> Of all patients seen between 1931 and 1934 inclusive, 57 per cent of those having carcinoma of the rectum and 55 per cent of those having carcinoma of the colon were subjected to resection. The combined operative mortality was 14.5 per cent. The five-year survival rate among resected cases was 44 per cent for the rectal group and 54 per cent for the colon group. Of all cases, both resectable and nonresectable, the total salvage was 25 per cent in carcinoma of the rectum and 29.4 per cent in carcinoma of the colon. It is anticipated that, with the present operability figure now ranging around 85 per cent and with a somewhat smaller operative mortality, about one-third of all these patients may be expected to survive the five-year period. The five-year survival rate will not, however, increase proportionately with the rise in operability for not only does this latter reflect attempts at curing the more advanced and poorer risk patients whose prognosis is known to be bad, but it also indicates an attempt at palliation for some patients who are beyond hope of cure. Actually, 10 per cent of all resections are now done in the presence of liver metastases. It therefore seems unlikely at the present time that anything additional will be accomplished by this means.

#### FUTURE ADVANCES

Further advances can only result from more widespread attempts at earlier diagnosis. Swinton and Higginbotham<sup>26</sup> recently demonstrated in 300 patients with cancer of the rectum or colon that 97.5 per cent complained of some form of bowel dysfunction. Yet the average time elapsing before a correct diagnosis was made averaged nine to twelve months in the rectal and colon cases respectively. Comparison with a



similar study done five years earlier indicated that the diagnoses at present are being made no earlier than they were at that time. About 30 per cent of the patients with rectal disease seen at the clinic had been given treatment for hemorrhoids within six months prior to the establishment of the diagnosis of carcinoma. About 15 per cent of patients with right colon tumors are operated upon for appendicitis before a correct diagnosis is made. The truth of such figures is attested by the fact that only 15 to 30 per cent of the growths still remain limited to the bowel wall at the time of operation and may, therefore, still be considered early.

Nevertheless, the diagnosis of cancer of the large bowel is not difficult and can almost invariably be made by one of three simple procedures, which in relative order of importance are:

1. Digital examination.
2. Sigmoidoscopic examination.
3. Barium and contrast enema.

Since carcinoma of the rectum makes up a little more than 50 per cent of all malignant large bowel growths, digital examination alone will account for approximately that number. An additional 25 per cent may be diagnosed on sigmoidoscopy and the remainder by barium enema. Very occasionally suspicious but inconclusive roentgenologic findings will require exploratory laparotomy for verification.

The practice of ordering a barium enema without having done at least a digital examination has resulted in many a missed diagnosis because the negative x-ray report usually obtained induces a false sense of security. The late Dr. D. F. Jones frequently emphasized this.

What can be accomplished by early diagnosis has been clearly demonstrated in many recent reports dealing mainly with cancer of the rectum. As long as the growth remains confined to the rectal wall the chance of cure is better than 90 per cent. When the perirectal tissues become invaded and the nodes still remain free of disease, from 60 to 70 per cent probability of five-year survival still remains. After regional node involvement has taken place, however, the opportunity for cure falls to between 15 and 20 per cent.<sup>11</sup>

There is little doubt that many if not all cancers of the large bowel originate as benign polyps. Junghanns<sup>15</sup> found evidence to support this relationship in 70 per cent of cases of carcinoma of the colon studied. On the other hand, all benign polyps do not become malignant, though none may be relied upon to remain benign. Opinions vary as to what percentage eventually undergoes malignant change. Among those that do, however, there must exist a variable time period of transition which provides a precious margin of safety from the standpoint of diagnosis. Obviously then, a large measure of future success must depend on the more general search for, and recognition of, these precancerous lesions. Their high incidence should accordingly be mentioned. It probably ranges around 5 per cent (Susman,<sup>28</sup> 6 per cent; Stewart,<sup>27</sup> 4.19 per

cent). Lawrence<sup>19</sup> has reported the low figure of 2.37 per cent, but one-quarter of his cases were children. Feyrter<sup>8</sup> has reported an incidence of 21.5 per cent (probably too high) and has pointed out, as have others, the rising frequency of occurrence with advancing age. Such studies are based on large series of consecutive autopsies and may properly be considered to represent cross sections of the population.

The diagnosis of polyps depends largely on proctoscopy and the contrast enema. Even large rectal polyps may frequently be missed on digital examination because of their soft consistency. The discovery of polyps on digital or proctoscopic examination always calls for complete large bowel study by barium and contrast enemas, not only in the search for other polyps but to rule out carcinoma. Such enemas should be repeated at appropriate intervals probably not greater than six months in order to detect the development of carcinoma in its incipency. Accessible polyps should be dealt with locally and here fulguration alone or, sometimes better, combined with low penetration irradiation of their base is indicated. Bulky polyps of the colon may be treated by colotomy and local removal.<sup>5</sup> It should be mentioned here that in any exteriorization resection procedure done on the colon, closure of the resultant colostomy should not be accomplished until both loops have been colonoscoped as far as is possible and all polyps destroyed.

#### SUMMARY

1. The discouraging results of irradiation therapy and the high incidence of regional node metastases have greatly clarified the surgical problem involved in the treatment of carcinomas of the colon and rectum.

2. Increasing radicalness in the removal of the primary tumor as well as of the lymphatics draining it has been the result as indicated by a steadily rising operability rate.

3. Much credit for making this possible is due to the advantages of the two-stage rectal resection.

4. The accompanying decrease in postoperative mortality is largely attributed to more careful preoperative preparation, increasing operative experience, and the employment of certain measures aimed at preventing the more serious postoperative complications.

5. The end results in patients treated during the years 1931 to 1934 inclusive have been cited and the hope expressed that with the more recently increased operability even a greater number will be permanently benefited.

6. Any appreciable future advances, it is believed, can be made only through more widespread attempts at earlier diagnosis.

7. The role of intestinal polyps in the development of carcinoma is discussed.

#### REFERENCES

1. Allen, A. W.: Right Colectomy for Malignant Disease, *J. A. M. A.* 109: 923-928, 1937.

2. Berven, E.: Radiological Treatment of Cancer of the Rectum, *Acta radiol.* 20: 373-390, 1939.
3. Binkley, G. E.: Results of Radiation Therapy in Primary Operable Rectal and Anal Cancer, *Radiology* 31: 724-728, 1938.
4. Cattell, R. B.: End-Results in Cancer of the Large Bowel, *Northwest Med.* 39: 438-441, 1940.
5. Cattell, R. B., and Swinton, N. W.: The Diagnosis and Treatment of Sigmoidal Polyps, *New England J. Med.* 222: 535-540, 1940.
6. Dixon, C. F.: Surgical Removal of Lesions Occurring in the Sigmoid and Rectosigmoid, *Am. J. Surg.* 46: 12-17, 1939.
7. Ewert, E. E.: A Comparative Analysis of the Urological Complications Following Large Bowel Surgery, *J. Urol.* 46: 764-776, 1941.
8. Feyrter, F.: Zur Lehre von der Polypenbildung im menschlichen Darm, *Wien. med. Wchnschr.* 79: 338-342, 1929.
9. Gabriel, W. B., Dukes, C., and Bussey, H. J. R.: Lymphatic Spread in Cancer of the Rectum, *Brit. J. Surg.* 23: 394-413, 1935.
10. Gilchrist, R. K., and David, V. C.: Lymphatic Spread of Carcinoma of the Rectum, *Ann. Surg.* 108: 621-642, 1938.
11. Gordon-Watson, C.: Origin and Spread of Cancer of the Rectum in Relation to Surgical Treatment, *Lancet* 1: 239-245, 1938.
12. Hand, L. V., and Sise, L. F.: Nupercaine Anesthesia, *Surg., Gynec. & Obst.* 71: 9-21, 1940.
13. Jones, D. F.: Carcinoma of the Rectum and Colon, *South. M. Jour.* 29: 339-344, 1936; *Bull. New York Acad. Med.* 12: 509-518, 1936.
14. Jones, T. E.: Operability in Cancer of the Rectum, *Surg., Gynec. & Obst.* 66: 925-926, 1938.
15. Junghanns, H.: Die Zottengeschwülste des Dickdarms und Mastdarms, *Ergebn. d. Chir. u. Orthop.* 28: 1-71, 1938.
16. Lahey, F. H.: Two-stage Abdominoperineal Removal of Cancer of the Rectum, *Surg., Gynec. & Obst.* 51: 692-699, 1930.
17. Lahey, F. H.: Carcinoma of the Colon, *S. Clin. North America* 11: 233-244, 1931.
18. Lahey, F. H., and Cattell, R. B.: A Two-stage Abdominoperineal Resection of the Rectum and Rectosigmoid for Carcinoma, *Am. J. Surg.* 27: 201-213, 1935.
19. Lawrence, J. C.: Gastrointestinal Polyps; Statistical Study of Malignancy Incidence, *Am. J. Surg.* 31: 499-505, 1936.
20. Nicholson, M. J.: Pontocaine-glucose Solution for Spinal Anesthesia, *S. Clin. North America* 20: 639-646, 1940.
21. Pemberton, J. deJ., and Whittaker, L. D.: Resection of the Right Half of the Colon, *Surg., Gynec. & Obst.* 65: 92-99, 1937.
22. Rankin, F. W.: The Choice of Operative Methods for Carcinoma of the Rectum, *SURGERY* 7: 667-673, 1940.
23. Schreiner, B. F.: Successful Irradiation Treatment of Eight Cases of Inoperable Rectal Carcinoma, *Am. J. Cancer* 24: 326-333, 1935.
24. Shedden, W. M., and Dresser, R.: Carcinoma of the Colon (Exclusive of the Rectum), *Am. J. Roentgenol.* 43: 715-725, 1940.
25. Simmons, H. T.: Retention of Urine Following Excision of the Rectum, *Brit. M. J.* 1: 171-172, 1938.
26. Stewart, F. W., and Farrow, J. H.: The Radiosensitivity of Tumors. In: *The Treatment of Cancer and Allied Diseases*, New York, 1940, Paul B. Hoeber, p. 109.
27. Stewart, M. J.: Precancerous Lesions of the Alimentary Tract, *Lancet* 2: 669-675, 1931.
28. Susman, W.: Polypi Coli, *J. Pathl. & Baet.* 35: 29-33, 1932.
29. Swinton, N. W., and Higginbotham, J.: The Diagnosis of Carcinoma of the Colon and Rectum, *S. Clin. North America* 18: 733-743, 1938.
30. Westhues, H.: Die pathologisch-anatomischen Grundlagen der Chirurgie des Rektumkarzinoms, Leipzig, 1934, G. Thieme, 113 pp.

# Review of Recent Meetings

---

## REVIEW OF THE SOUTHERN SURGICAL ASSOCIATION MEETING, DECEMBER 9-11, 1941, PINEHURST, N. C.

D. HENRY POER, M.D., ATLANTA, GA., AND GUY W. HORSLEY, M.D.,  
RICHMOND, VA.

*(From the Departments of Surgery, Emory University, and Medical College of  
Virginia)*

THE FIFTY FOURTH Annual Session of the Southern Surgical Association was held December 9, 10, and 11, 1941, at the Carolina Hotel, Pinehurst, N. C. Attendance was the largest in the Association's history with 154 members and 170 visitors and guests registered. Thirty seven of the forty listed papers were read.

H. H. Kerr, Washington, D. C., gave the Presidential Address during the annual banquet of the Association and discussed the Importance of Proper Selection of Men for Our Armed Forces during the present conflict. He stressed the need for more complete psychiatric examinations to weed out the mentally unfit since this group has become such an economic liability since World War I. He also discussed the surgical program for the present mobilization and improved treatment methods that have done much to lower mortality and restore injured soldiers to front line service in a minimum time.

J. D. Rives, New Orleans, La.: **Anatomy of the Attachments of the Diaphragm and the Relation of these Attachments to the Problems of the Surgery of Diaphragmatic Hernia**—Causes of diaphragmatic hernia were found to be (1) defects in the development of the diaphragm, (2) trauma, and (3) infection. The author noted that the weak gap in the development of the diaphragm was found more frequently in the left side. He described methods for operative relief of anterior defects which was accomplished by dissection of the trans versus muscle allowing the diaphragm to be pulled over the defect. Thus the muscle becomes part of the diaphragm. Omentum was used to cover raw area. For closure of posterior defects he suggested resection of the tenth rib, sliding a flap of the latissimus dorsi muscle over the defect and suturing it to the margin of the diaphragm. Results were satisfactory after a 2 year period.

S. W. Harrington, Rochester, Minn.: **Diaphragmatic Hernia**.—The results of a study of diaphragmatic hernia in children was presented and compared with the same condition in adults. He noted that from 1908 to 1923 there were only 31 cases at the Mayo Clinic, two being in children, but from 1926 to 1941 there were 700 cases, 304 of which came to operation. Of these 283 were in adults with eleven deaths and 24 in children, with four deaths. The majority of all deaths were caused by cardiorespiratory disease often associated with pneumonia or pulmonary collapse. He noted an increasing hazard of the operation as the child grew older and advocated surgery as soon as the diagnosis was made. Management of diaphragmatic hernia in children was different because most were due to congenital developmental defects, while the hiatus hernia was frequently seen in adults. The short esophagus and pleuroperitoneal diaphragm types were observed in children.

Received for publication Jan. 22, 1942

Discussion: A. O. Singleton, Galveston, Texas, pointed out the need for the roentgeologist becoming more "conscious" of diaphragmatic hernia. He questioned the point of approach and preferred the transthoracic without removal of the ribs, to the abdominal. He found the cases with congenital absence of a portion of the diaphragm most difficult to repair and mentioned the use of large pieces of autogenous graft. In closing, Rives stated that he approached this type through the abdomen using transplants of the transversalis abdominis muscles attached to the dome of the diaphragm. Harrington also approached this type through the abdomen. He stated that the phrenic nerve should be interrupted in most cases.

3. A. W. Allen, Boston, Mass.: **Gastric Resection for Duodenal Ulcer: Follow-Up Studies.**—Of 2726 cases of duodenal ulcer treated at the Massachusetts General Hospital, 588 or 21 per cent had surgical methods used. Operation was performed for perforation in 24.3 per cent, for obstruction in 32.8 per cent, and for pain or hemorrhage in 31.9 per cent. Posterior gastroenterostomy and resections were done in the same number of cases with identical mortality (9.3 per cent). The popularity of resections has increased during the past 4 years with a corresponding decrease in the number of posterior gastroenterostomies. Sixty-seven marginal ulcers were observed following posterior gastroenterostomy, two as late as 18 years although two-thirds of the whole occurred within 2 years of operation. The results following the Finsterer exclusion operation were poor, and only fair following pylorotomy, but were noted to be good following subtotal resection.

Twenty-six resections were performed since 1938 with five deaths, and one poor result. Other cases are apparently cured. Peritonitis, pneumonia, hemorrhage, fistula, and stricture of the common duct caused the complications observed in this series. Allen concluded that the results were better and the mortality lower following subtotal resection, provided at least one-half of the stomach and the pylorus including the pyloric sphincter are removed.

4. Waltman Walters, Rochester, Minn.: **Gastric Ulcer or Ulcerating Carcinoma (abstract).**—It was noted that some gastric ulcers heal satisfactorily but that many recur at a later date. No conclusive evidence concerning the healing of chronic ulcers under medical treatment could be found. Roentgenography and gastroscopy could not be relied upon entirely to exclude malignancy and the author cited illustrative cases. Since gastric acidity and tissue susceptibility cannot be continuously controlled under a medical regime, he considered recurrences understandable. In proved cases of gastric carcinoma, the first symptom was that of ulcer in 33 per cent and an "effective" response to medical treatment was obtained in 80 per cent of cases of cancer with ulcer symptoms. The diagnostic value of gastric acidity was lessened when he found that only 50 per cent of patients who had carcinoma had gastric anacidity and that in 20 per cent of the cases the value for the gastric acidity was as much as 30 according to the method of Töpfer. Walters preferred gastric resection for treatment of large chronic ulcers that do not respond to medical treatment. He called attention to the fact that a roentgenographic report of gastric ulcer had been made concerning 10 per cent of a large group of patients operated on for cancer of the stomach.

Discussion: F. W. Baneroff, New York, N. Y., described an interesting case of ulcer on the lesser curvature in which one-half of the ulcer was found to be malignant at operation in 1930. A second operation recently performed revealed a marginal ulcer with hemorrhage. He advocated coring out of the mucous membrane of the pylorus when its removal is impractical, and also included a part of the normal stomach. R. L. Sanders, Memphis, Tenn., also had observed the increasing popularity of gastric resection for chronic ulcer in comparison to

posterior gastroenterostomy and stated that his results justified the change. He stressed the importance of removal of the pylorus to insure good results. R. L. Payne, Norfolk, Va., discussed the problem of closure of the duodenal stump and requested information in regard to preventing a duodenal fistula. In closing, Allen emphasized the necessity of performing a complete operation including removal of the pylorus. To prevent duodenal fistula, he stated that enough cuff of bowel was needed for two rows of sutures for infolding and advocated a two-stage procedure if necessary. Walters stated that the results of gastric resection for chronic gastric ulcer were almost perfect, but, when partial gastrectomy was performed for duodenal ulcer, in his experience, recurrence took place in 2 per cent of the cases.

5. Mims Gage, New Orleans, La.: **Aneurysm of the Abdominal Aorta: Failure of Obliteration by Ligation (abstract).**—A review of the literature on ligation of the abdominal aorta for aneurysm was outlined. The author reported a case of aneurysm of abdominal aorta in which he ligated the abdominal aorta above the bifurcation with cotton tape. The pulsations returned in the aneurysm sac. Three months after ligating the aorta, he ligated the right common iliac with three ligatures. It was then discovered, due to shrinkage of the sac, that the aneurysm was one occurring at the bifurcation of the common iliac which had ruptured. Both procedures failed to cure the aneurysm. Gage reviewed 35 cases and found that syphilis and arteriosclerosis were the chief causes of weakness of the aortic wall that resulted in aneurysm formation. Signs and symptoms included pain, the presence of tumor (expansile pulsation 50 per cent), pulsation of the tumor, and a bruit. Experimentally, the dog's aorta (which cannot be compared to the human aorta) had been occluded with: (1) round ligatures, (2) flat cotton tape, (3) metal bands, clamp and compressors, wire, tin, and aluminum, (4) rubber bands, spring devices, fascia plugs, cellophane, and sclerosing solutions. In the human being, ligatures have consisted of cotton tape, braided silk, fascia lata and aluminum bands, intra-aortic plugs of fascia, and steel springs. Complications usually result from rupture of aorta at the site of the ligature (especially round ligatures and metal bands) or the aneurysm sac itself. Paralysis of the legs and urinary bladder does not infrequently occur but fortunately is a temporary affair. Gangrene also occurs following ligation and is due to inefficient collateral circulation. This is a very serious complication. Sudden elevation of the blood pressure occurs, with acute dilation of the heart. Decreased cardiac output and embolism also may result. Treatment requires adequate development of collateral circulation plus obliteration of the aorta and aneurysm sac. In aneurysms of the bifurcation, lumbar sympathectomy of the thoracic aorta (Smithwick's thoracoabdominal procedure) is advocated.

6. James C. Owings, Baltimore, Md.: **Successful Experimental Ligation and Division of the Thoracic Aorta.**—The successful ligation and division of the thoracic aorta in four experimental animals (dogs) was described. The author reviewed Hnlsted's experimental work and considered his failure to be due to the fact that (1) the change in the caliber of the vessel was produced too abruptly and (2) a nonyielding material was used. He used wide rubber bands which yielded sufficiently to prevent cutting through of the vessel wall and yet produced gradual compression of the vessel. The bands were applied in three stages and the vessel divided after about three or four months when collateral circulation was sufficiently developed.

Discussion: Harvey B. Stone, Baltimore Md., emphasized the importance of this work citing the new conceptions of vascular surgery that had resulted from it. Barney Brooks, Nashville, Tenn., likewise mentioned the value of these experiments and stated that possibly the hypertension produced may be due to the same causes as that produced by the Goldblatt clamp in cutting of the

Discussion: A. O. Singleton, Galveston, Texas, pointed out the need for the roentgenologist becoming more "conscious" of diaphragmatic hernia. He questioned the point of approach and preferred the transthoracic without removal of the ribs, to the abdominal. He found the cases with congenital absence of a portion of the diaphragm most difficult to repair and mentioned the use of large pieces of autogenous graft. In closing, Rives stated that he approached this type through the abdomen using transplants of the transversalis abdominis muscles attached to the dome of the diaphragm. Harrington also approached this type through the abdomen. He stated that the phrenic nerve should be interrupted in most cases.

3. A. W. Allen, Boston, Mass.: **Gastric Resection for Duodenal Ulcer: Follow-Up Studies.**—Of 2726 cases of duodenal ulcer treated at the Massachusetts General Hospital, 588 or 21 per cent had surgical methods used. Operation was performed for perforation in 24.3 per cent, for obstruction in 32.8 per cent, and for pain or hemiorrhage in 31.9 per cent. Posterior gastroenterostomy and resections were done in the same number of cases with identical mortality (9.3 per cent). The popularity of resections has increased during the past 4 years with a corresponding decrease in the number of posterior gastroenterostomies. Sixty-seven marginal ulcers were observed following posterior gastroenterostomy, two as late as 18 years although two-thirds of the whole occurred within 2 years of operation. The results following the Finsterer exclusion operation were poor, and only fair following pylorotomy, but were noted to be good following subtotal resection.

Twenty-six resections were performed since 1938 with five deaths, and one poor result. Other cases are apparently cured. Peritonitis, pneumonia, hemiorrhage, fistula, and stricture of the common duct caused the complications observed in this series. Allen concluded that the results were better and the mortality lower following subtotal resection, provided at least one-half of the stomach and the pylorus including the pyloric sphincter are removed.

4. Waltman Walters, Rochester, Minn.: **Gastric Ulcer or Ulcerating Carcinoma (abstract).**—It was noted that some gastric ulcers heal satisfactorily but that many recur at a later date. No conclusive evidence concerning the healing of chronic ulcers under medical treatment could be found. Roentgenography and gastroscopy could not be relied upon entirely to exclude malignancy and the author cited illustrative cases. Since gastric acidity and tissue susceptibility cannot be continuously controlled under a medical regime, he considered recurrences understandable. In proved cases of gastric carcinoma, the first symptom was that of ulcer in 33 per cent and an "effective" response to medical treatment was obtained in 80 per cent of cases of cancer with ulcer symptoms. The diagnostic value of gastric acidity was lessened when he found that only 50 per cent of patients who had carcinoma had gastric anaecidity and that in 20 per cent of the cases the value for the gastric acidity was as much as 30 according to the method of Töpfer. Walters preferred gastric resection for treatment of large chronic ulcers that do not respond to medical treatment. He called attention to the fact that a roentgenographic report of gastric ulcer had been made concerning 10 per cent of a large group of patients operated on for cancer of the stomach.

Discussion: F. W. Bancroft, New York, N. Y., described an interesting case of ulcer on the lesser curvature in which one-half of the ulcer was found to be malignant at operation in 1930. A second operation recently performed revealed a marginal ulcer with hemiorrhage. He advocated coring out of the mucous membrane of the pylorus when its removal is impractical, and also included a part of the normal stomach. R. L. Sanders, Memphis, Tenn., also had observed the increasing popularity of gastric resection for chronic ulcer in comparison to

Preliminary ligation of the splenic artery and a systematic control of the circulation of the spleen before it is delivered out of the abdomen assures an almost bloodless operation. The splenic bed is readily approached for the control of the oozing vessels before closure of the abdomen is done. Illustrations and motion pictures were given to clarify these statements.

11. Joseph E. J. King, New York, N. Y.: Oxycephaly (abstract).—A description of the operation first proposed and carried out by the author in 1936 was given and the details of 4 cases presented. Two of these were operated upon by Barnes Woodhall of Duke University Hospital by the same method. The condition of oxycephaly is due to premature closure of the suture lines, and unless the process is arrested these patients never reach adulthood. The symptoms and signs are headaches, irritability, marked exophthalmos, failing vision, convulsions, and finally loss of eyeballs and life. Roentgenograms show marked similarity in all cases, i.e., generalized convolutional markings, depression of the fossae of skull, narrowing and deepening of the sella turcica, shallowness of orbits, absence of suture lines, and protrusion of lower jaw. The author described the method of surgical procedure used in his cases, which consisted of morcellation of the calvarium produced by making many burr hole openings, and cutting between them with a DeVilbiss rongeur to create numerous skull segments which readily adapted themselves in conformation position. This resulted in correction of the deformity and relief of the symptoms. The results were satisfactory.

Discussion: M. B. Woodhall, Durham, N. C. mentioned the 2 types of this condition, viz., (1) craniofacial with hyperplasia of the maxilla, and (2) skull deformity. He had operated upon three patients with restoration of cranial symmetry. He included subtemporal decompression in his operative procedure.

12. Claude C. Coleman, Richmond, Va.: Treatment of Compound Fracture of the Skull (abstract).—The main emphasis was placed on the importance of early complete operation on all open wounds of the head. The principles of treatment for contused laceration of the scalp were the same as those employed for more severe injuries such as compound fractures with laceration of the dura and damage to the brain. Coleman has found from analyses of several large series of acute head injuries that shock, as determined by clinical examination and blood pressure estimation, develops in less than 10 per cent of the total number of cases admitted to his clinic. Early operation, that is within 6 to 8 hours, can be done in a large majority of cases of compound fracture of the skull. If shock is present, treatment should be directed to this condition and everything avoided that would tend to increase shock. If complete operation is delayed because of shock, he advocated shaving the scalp around the wound, controlling external hemorrhage, dusting the wound with sulfanilamide crystals, and applying a sterile bandage. He further emphasized the thorough disinfection of the wound by large quantities of sterile solutions and the avoidance of chemicals. Macerated brain tissue, blood clot and other debris should be removed by the suction apparatus and hemorrhage carefully controlled. Another point stressed in the paper was the importance of closing the dura in all cases in which it has been torn by the fracture. Closure of the dura, he said, was especially important in fracture involving the frontal and ethmoid sinuses. Drainage has not been used by the writer in such cases. Chemotherapy is advocated in the treatment of all cases with dural penetration and in fractures of the base when it is believed that the dura has been lacerated. In a series of 224 compound fractures the total mortality was 16.5 per cent with operative mortality of 12 per cent.

Discussion: Chalmers H. Moore, Birmingham, Ala., stated that he used opposite methods of treatment. Shock was present in most of the patients seen by him and operation was delayed. At the end of 24 hours operation was carried out in the manner described by the author.



blood supply to the kidney. In closing, Owings stated that study of the kidneys showed normal function and section and the hypertension therefore was not the same as that produced by the Goldblatt clamp. He stated that the rubber bands stay when they are placed and maintain their elasticity, but occasionally a band had cut through the vessel.

7. **George G. Finney** (and **John K. Owen**, by invitation), Baltimore, Md.: **The Surgical Aspect of Congenital Absence of the Gall Bladder with Report of Two Cases** (abstract).—Reports of forty-six instances of congenital absence of the gall bladder without any congenital anomaly were found in the literature by the authors and 2 cases were added. Stones were found in the ducts in the 11 cases where full data was given. The common duct was usually dilated with obstruction of the ducts, pain, and jaundice. The first patient, a 68-year-old male, entered the hospital complaining of acute abdominal pain thought to be produced by biliary colic. He had an old ulcer history dating back some 10 or 12 years. At operation, exploration revealed the scar of an old ulcer, but no gall bladder could be located. The common bile duct was dilated only slightly, but when opened, two imbedded stones were removed. The second patient, a female 69 years of age, also had abdominal pain indicative of biliary colic and evidence of cardiac decompensation. No gall bladder was found at operation and the common bile duct was dilated and contained two stones. The first patient recovered but the second one died 24 hours after operation due to cardiac failure. Autopsy revealed no evidence of gall bladder either extra- or intrahepatic. **Hugh H. Trout**, Roanoke, Va., told of a case in which gall bladder visualization showed evidence of a double gall bladder, only one of which contained stones.

8. **Harold L. Foss**, Danville, Pa.: **Intestinal Obstruction Due to Gall Stones.**—The high mortality resulting from intestinal obstruction caused by gall stones was pointed out by the author and the frequency of such obstructions among all obstructions was found to be 4 per cent in his clinic. The stone usually passes by cholecystenteric fistula. Symptoms were those of ileus and may be absent or intermittent. Stones usually lodge in the lower ileum (78 per cent), but also have been found in other portions of the intestine or colon. The duration of the obstruction before hospital admission of the author's 10 cases was 5.2 days and the mortality 50 per cent. Delay was mentioned as the chief cause of the high mortality.

Discussion: **Edward V. Mastin**, St. Louis, Mo., presented 5 cases in which gall stones caused intestinal obstruction and advocated loop ileostomy as a method of lowering the high mortality. This was successful in the 3 of his cases in which it was used. **George G. Finney**, Baltimore, Md., added 3 cases with one death. One of these had two operations.

9. **Edwin P. Lehman**, Charlottesville, Va.: **Annular Pancreas as a Clinical Problem** (abstract).—A case of annular pancreas, one of 48 in the literature, was reported. A discussion of the clinical aspects of the 9 previous cases that had come to operation was given and a case presented which was the first in which the diagnosis was made before operation. The anomaly is the result of incomplete migration of the ventral anlage and apparently creates symptoms only when pancreatitis occurs. The symptoms are those of chronic duodenal obstruction. Although posterior gastroenterostomy has been the more popular operation, direct division of the ring with or without resection is advised.

10. **A. O. Singleton**, Galveston, Texas: **Splenectomy.**—The indications for splenectomy are given and also a technical presentation which is calculated to lessen the operative mortality in splenectomy. A lateral transverse incision is given which is anatomic in most details and gives excellent exposure of the operative field. This incision not only gives good exposure of the operative field but preserves the integrity of the abdominal wall.

From his experience he stated while age is a hazard it should not be considered a contraindication to operation. Occasionally he thinks it is advisable to operate on patients where there are one or two doubtful nodules in the liver which may be metastases but also could be benign tumors of the liver such as adenomas or angiomas. The life expectancy of patients with definite liver involvement is about 10 months. Even though marked obesity makes the case more difficult, it is certainly not a contraindication. Sixty-five per cent of the patients with cancer of the rectum will show lymph gland involvement. The one-stage combined abdominal perineal resection is the operation of choice and in the last five years there have been only four two-stage operations as against 112 one-stage operation.

Discussion: F. W. Rankin, Lexington, Ky., agreed that everything should be done to extend the operability in these cases. He considered the one-stage modified Miles operation to give the best results, with an operation mortality of 5 per cent to 10 per cent. Harvey B. Stone, Baltimore, Md., stressed the value of the one-stage operation but when attempting to extend the indications for operability he varied the procedure. W. B. Marbury, Washington, D. C., discussed the use of a tube through a cecostomy in order to clean out the bowel if obstruction had taken place. He noted a lower infection percentage following this procedure. In closing, David pleaded for giving all doubtful cases a chance, since the nonoperative treatment is hopeless.

16. John E. Cannaday, Charleston, W. Va.: The use of the Cutis Graft in the Repair of Certain Types of Incisional Herniae (abstract).—Cutis takes on the function of either fascia or tendon if grafted between or in place of these structures. In obtaining the graft either Thiersch or split skin grafts are first taken from the donor site after which a graft of suitable size and shape is taken from the underlying derma including a layer of fatty tissue underneath about one centimeter in thickness. This constitutes the cutis graft. After the graft has been sutured into its new location and the repair operation has been completed, the area from which the graft has been taken is repaired either by closure with interrupted tension sutures or, in case a split skin graft has been removed, the latter is secured in place so as to cover the raw surface. If the cutis graft is to be used for repair of hernia or for replacement of tendon the thick graft from which the epidermis only has been removed is more satisfactory. In Cannaday's opinion, cutis has longer life than fascia, takes more readily, is not more liable to infection, and is more readily available. He particularly prefers it to fascia in the repair of large incisional hernias, especially in cases in which it is impossible to overlap the edges of the hernial opening. Cutis makes an excellent suture or ligature material and can be used satisfactorily in varied types of general surgery, also in bone and joint surgery for the replacement of ligaments, and in the reconstruction of joints of the long bones. It is of especial value in the filling out of defects in plastic surgery about the face, and for replacement purposes in certain cases of delayed skin transplantation. Both sulfanilamide and sulfathiazole, either singly or in combination, and cotton thread sutures were used in the performance of the operations described. A short film was shown illustrating the technique and repair of a large incisional hernia. Six consecutive cases were reported, in each of which primary union with satisfactory results had been secured.

17. Joseph D. Collins, Portsmouth, Va.: A Method of Disposal of the Sac in Operations for Oblique Inguinal Hernia (abstract).—The inguinal canal having been opened by incising the aponeurosis of the external oblique, the sac is dissected upwards from its bed and freed from its attachments to the cord and cremaster muscle. Any adherent abdominal viscera is released and allowed to drop back into the abdominal cavity. An over-and-over silk suture is passed

13. **Walter E. Dandy, Baltimore, Md.:** **The Diagnosis and Treatment of Ruptured Intervertebral Disc.**—Pertinent facts regarding the diagnosis of ruptured intervertebral discs based on careful study of signs and symptoms were presented. Dandy considered lipiodol and air injections unnecessary and frequently harmful because they could not disclose the lesion. He reviewed the history of the development of the operation for the relief of this condition, pointing out the fact that it has now been simplified and is performed without harm or risk. The question of "concealed discs" was discussed since 25 per cent of his series were of this type. He states that relief following operation was immediate or slow but permanent in his cases. Sixty-three cases had been operated upon in the past 8 months, a ruptured disc being found in each instance.

**Discussion:** **Chalmers H. Moore, Birmingham, Ala.,** brought out the "compensation factor" in a series of 200 cases. The results of operation were good in 90 per cent without compensation, and bad in 85 per cent with compensation. He had similar experiences in 26 personal cases. **George E. Bennett, Baltimore, Md.,** discussed the causes of low back pain and sciatica and outlined the many procedures carried out for their relief including manipulation, arthrodesis of sacroiliac joint, lumbosacral fusion, fasciotomy tenotomy of piriformis muscle, and the removal of ruptured intervertebral discs. **J. E. J. King, New York, N. Y.,** requested information concerning hypertrophy of ligamentum flavum and also stated that if lipiodol is injected it should be removed on the same day. Dandy, in closing, stated that he was not convinced of the occurrence of hypertrophy of the ligamentum flavum. He also made the point that the backache due to rupture of intervertebral disc is recurrent and not constant.

14. **L. Wallace Frank, Louisville, Ky.:** **Sarcoma of the Small Intestine.**—A review of the recent literature on sarcoma of the small bowel showed the average age to be between 40 and 42. The symptoms are those of gradual obstruction associated with severe nausea and vomiting depending on the location of the lesion. Reports of 4 cases were given: (1) a spindle cell sarcoma in the terminal ileum, (2) a reticulum cell sarcoma in the jejunum—this case had symptoms of a duodenal ulcer and also bleeding from the bowel, (3) a lymphosarcoma in the jejunum 14 inches below the ligament of Treitz—this patient was a boy, aged 18 years who was thought at first to have an appendical abscess, and (4) a neurofibrosarcoma of the jejunum of an annular constriction type. All cases reported since 1932 were reviewed with the addition of these 4 new cases.

15. **Vernon C. David, Chicago, Ill.:** **Extension of the Indications for Radical Operation in Cancer of the Rectum (abstract).**—One of the chief problems in the radical operation for cancer of the rectum is to increase the limits of resectability. In those cases not operated upon the mortality is 100 per cent. David reported a series of 277 cases of which 179 had the tumor removed with a mortality rate of 7.2 per cent. One-hundred twenty-nine had a one-stage combined perineal resection, and there were 22 other cases which had obstruction resections or local removal of the tumor. The chief cause for inoperability is definite metastasis to the liver, fixation of the growth to the base of the bladder, or infiltration of the soft parts, particularly the prostate, rectovaginal septum and sacrum. In many cases the fixation of the tumor mass to the bladder, prostate or rectovaginal septum has not advanced to the point where resection of these various organs and tissues cannot be done at the same time radical resection of the rectum is carried out. There was only one patient who was refused operation on account of age. This patient was 81 years old and also had bronchitis. In this instance a colostomy alone was done. David's report shows that 38 patients over 65 years of age had removal of the tumor, with four deaths. There were: 18 between the ages of 65 to 70; 12 between the ages of 70 to 75; 4 between the ages of 75 to 80; and 4 between the ages of 80 to 85.

Green, Houston, Texas, stated that the choice of anesthetic is quite important to prevent strain immediately after operation. In his opinion spinal anesthetic is the one of choice. R. D. Jones, Jr., Norfolk, Va., stated that for many years he and Dr. Payne had been using fascia from the external oblique, the advantage being that no separate incision would have to be made to obtain the fascia and its use, in his opinion, lowers the incidence of the recurrence. A. R. Koontz, Baltimore, Md., stated the army regulations at the present are different and that hernia is not considered to be present unless the sac can be definitely demonstrated. A large opening of the inguinal canal is not considered to be a contraindication to military service. In his opinion large sheets of ox fascia which have been preserved have all the advantages of either autogenous fascia or cutis grafts and none of the objections. However, he called attention to the fact that the ox fascia is in a preservative and this must be washed out with a saline solution for two hours or more before using. He stated that at one time the preservative used for the ox fascia was inferior, however, this objection has now been overcome and within the last few years there has been no difficulty in this respect.

19. Warfield M. Firor, Baltimore, Md.: Succinyl Sulfathiazole: A New Intestinal Antiseptic.—One year ago the author reported on his experience in the use of sulfanilylguanidine with particular emphasis on whether it renders surgery on the large bowel safer. Since then the use of this drug has been discontinued because (1) the drug is absorbed and the low blood level is due to its rapid urinary excretion, (2) the drug is erratic in its action, and (3) the drug is toxic. Since that time, E. M. Poth investigated various other sulfonamide drugs and finally settled on succinyl sulfathiazole which has been used in 125 different cases. From their experience (Firor and Poth) they conclude that (1) it alters the physical content of the bowel, rendering it soft and odorless, and (2) it lowers the concentration of certain pathogenic organs such as *B. coli*, *Flexner*, *Shiga*, and *Sonne*. The succinyl radical prevents absorption. The bactericidal action is apparently due to gradual liberation of the sulfathiazole in the bowel. The dosage is 0.25 Gm. per kilogram every 24 hours. The drug is generally given in divided doses every 4 to 6 hours and should be started 3 to 7 days before operation and continued two weeks postoperatively. Of the 125 patients in whom it was used, it was effective in all but six. Of these six, three had increased diarrhea, two had an increased amount of bleeding from an ulcerated carcinoma of the colon and one had postoperative bleeding. In the latter case only 150 cc of blood were lost and there was no further complication. They emphasize the fact that it should be understood that this drug is an adjunct and not a substitute for asepsis.

Discussion E. M. Poth, Baltimore, Md., suggested that one of the soluble sulfonamide drugs be used just previous to operation in order to saturate the tissues. Succinyl sulfathiazole is not effective in the typhoid and paratyphoid group but it is very efficient with bacillary dysentery. Twenty cases of bacillary dysentery have been treated and all completely recovered in 24 to 48 hours. Attention was called to the fact that this drug did not effectively sterilize the bowel if there were blind ends or pouches and it was impossible for the drug to reach the bacteria in such conditions. E. P. Lehman, Charlottesville, Va., used the drug about three weeks and while his experiences were not enough to warrant any conclusion, his observations were similar to those of the authors and in all cases the blood level remained low. Firor, in closing the discussion, stated that in cases of colostomy or blind pouches, succinyl sulfathiazole could be given both by mouth and as enema irrigations.

20. Deryl Hart, Durham, N. C.: Disinfection of the Air in the Operating Room with Bactericidal Radiant Energy. Correlation of the Intensity of Radiation with Its Bactericidal Effect.—Statistics show marked lowering of infection

around the edge of the open end of the sac, completely encircling it, and this suture is tied loosely with a single knot and laid aside. The index finger is then inserted into the open mouth of the sac and passed through the neck of the sac into the peritoneal cavity, where it is made to impinge firmly against the anterior abdominal wall at a point two inches above the upper border of the internal ring. The fibres of the internal oblique and transversalis muscle over the impinging finger are then separated down to the transversalis fascia for a distance of an inch and a half. This separation is held apart by retractors. With curved Kelly forceps, a puncture is made through the transversalis fascia and peritoneum over the impinging finger, and the point of the blades of the forceps is pushed down through the internal ring, hugging the anterior abdominal wall and in contact with the tip of the finger until it emerges from the mouth of the sac. The suture in the mouth of the sac is drawn tightly around the blades of the Kelly forceps and the knot tied. The Kelly forceps are opened sufficiently to grasp the end of the tied suture and closed. The forceps, grasping the end of the tied sutures, are then withdrawn from the punctured opening in the transversalis fascia and peritoneum, drawing the sac through the opening, thereby inverting it. When the sac is thick and bulky, the opening may have to be enlarged to permit this procedure. The inverted sac is then pulled outward with sufficient tension to eliminate any redundancy in the parietal peritoneum and thus abolish the hernial fossa. The sac is transfixed and ligated, the excess distal to the ligature being excised. The stump of the sac is then sutured to the edge of the opening of the transversalis fascia and peritoneum with a figure of eight suture. The opening in the oblique and transversalis muscles is closed with several interrupted sutures. The inguinal canal is then repaired according to the desires of the surgeon.

18 Edward V. Mastin, St. Louis, Mo. **An Operation for the Repair of Inguinal Hernia**—Surgeons are able to close hernia satisfactorily in the lower angle but many recurrences are due to weakness about the internal inguinal ring. Mastin suggested a new type of closure of the internal ring after the usual suturing of Poupart's ligament to the conjoint tendon and internal oblique muscle. An incision is made in the upper part of the internal oblique muscle just over the internal opening and the cord is brought out through this incision. The muscles on the outside of the cord can be closed so that there is no constriction on the vessels of the cord. The aponeurosis of the external oblique is then closed with the cord being brought out in a similar manner through this fascia. This places the cord on the outside of the external oblique and completely obliterates the middle of the inguinal canal.

**Discussion.** C. R. Robins, Richmond, Va., stressed the importance of exposing the pubic insertion of the rectus abdominal muscles as, in his opinion, most recurrences occur in the lower part of the incision and are due to weakness or absence of the conjoint tendon. W. F. Rienhoff, Baltimore, Md., stated that, contrary to the findings of Mastin, most recurrences at Johns Hopkins Hospital occurred in the lower part of the incision, which he thinks is due to the absence of the conjoint tendon. To cover this defect the fascia from the rectus can be slid over, not turned over, and sutured in place. Bradley L. Coley, New York, N. Y., believes the recurrences are due to a number of factors, especially to defects of the tissues in this area. He stressed the importance of the proper suturing of the transversalis muscles. He also called attention to the mistakes which were made by the examining physicians during the first World War and stressed the importance of avoiding them in the present emergency. In his opinion a patient who has large inguinal rings but no hernia should not be subjected to an operation because the majority of these patients will never develop a hernia and the operation is unnecessary and often unsuccessful. C. C.

Green, Houston, Texas, stated that the choice of anesthetic is quite important to prevent strain immediately after operation. In his opinion spinal anesthetic is the one of choice. R. D. Jones, Jr., Norfolk, Va., stated that for many years he and Dr. Payne had been using fascia from the external oblique, the advantage being that no separate incision would have to be made to obtain the fascia and its use, in his opinion, lowers the incidence of the recurrence. A. R. Koontz, Baltimore, Md., stated the army regulations at the present are different and that hernia is not considered to be present unless the sac can be definitely demonstrated. A large opening of the inguinal canal is not considered to be a contra indication to military service. In his opinion large sheets of ox fascia which have been preserved have all the advantages of either autogenous fascia or cutis grafts and none of the objections. However, he called attention to the fact that the ox fascia is in a preservative and this must be washed out with a saline solution for two hours or more before using. He stated that at one time the preservative used for the ox fascia was inferior, however, this objection has now been overcome and within the last few years there has been no difficulty in this respect.

19. Warfield M. Firor, Baltimore, Md: Succinyl Sulfathiazole: A New Intestinal Antiseptic.—One year ago the author reported on his experience in the use of sulfamylguanidine with particular emphasis on whether it renders surgery on the large bowel safer. Since then the use of this drug has been discontinued because (1) the drug is absorbed and the low blood level is due to its rapid urinary excretion, (2) the drug is erratic in its action, and (3) the drug is toxic. Since that time, E. M. Poth investigated various other sulfonamide drugs and finally settled on succinyl sulfathiazole which has been used in 125 different cases. From their experience (Firor and Poth) they conclude that (1) it alters the physical content of the bowel, rendering it soft and odorless, and (2) it lowers the concentration of certain pathogenic organs such as *B. coli*, *Flexner*, *Shiga*, and *Sonne*. The succinyl radical prevents absorption. The bactericidal action is apparently due to gradual liberation of the sulfathiazole in the bowel. The dosage is 0.25 Gm per kilogram every 24 hours. The drug is generally given in divided doses every 4 to 6 hours and should be started 3 to 7 days before operation and continued two weeks postoperatively. Of the 125 patients in whom it was used, it was effective in all but six. Of these six, three had increased diarrhea, two had an increased amount of bleeding from an ulcerated carcinoma of the colon and one had postoperative bleeding. In the latter case only 150 cc of blood were lost and there was no further complication. They emphasize the fact that it should be understood that this drug is an adjunct and not a substitute for asepsis.

Discussion E. M. Poth, Baltimore, Md, suggested that one of the soluble sulfonamide drugs be used just previous to operation in order to saturate the tissues. Succinyl sulfathiazole is not effective in the typhoid and paratyphoid group but it is very efficient with bacillary dysentery. Twenty cases of bacillary dysentery have been treated and all completely recovered in 24 to 48 hours. Attention was called to the fact that this drug did not effectively sterilize the bowel if there were blind ends or pouches and it was impossible for the drug to reach the bacteria in such conditions. E. P. Lehman, Charlottesville, Va., used the drug about three weeks and while his experiences were not enough to warrant any conclusion, his observations were similar to those of the authors and in all cases the blood level remained low. Firor in closing the discussion, stated that in cases of colostomy or blind pouches, succinyl sulfathiazole could be given both by mouth and as enema irrigations.

20. Deryl Hart, Durham, N. C.: Disinfection of the Air in the Operating Room with Bactericidal Radiant Energy. Correlation of the Intensity of Radiation with Its Bactericidal Effect.—Statistics show marked lowering of infection

following use of ultraviolet radiation in operating rooms. Several different types of installations of equipment were described. In the author's opinion, contamination of the air is the most important factor causing postoperative infection of clean wounds. He has noted that most infections occur during the months when respiratory infections are most frequent. In his opinion the entire room and the sterile supplies in the room should be irradiated and since proper irradiation has been carried out at Duke University Hospital, the infection rate has been lowered greatly and no fatal infection of clean wounds has occurred where radiation was used.

21. **Ralph G. Carothers, Cincinnati, Ohio: Sprained Ankles (abstract).**—The real pathology involved in the so-called sprained ankle is often a fracture or dislocation. Ability to rotate the astragalus after injection with novocain indicated dislocation according to his experience. Carothers discussed work on a cadaver showing that the astragalofibular ligament as well as the calcaneofibular ligament must be severed before the astragalus could be rotated in the mortise.

Discussion: **Clay Murray, New York, N. Y.**, stated that recurrent sprain of the ankle is not a sprain and that the astragalofibular ligament is never torn in sprains. Murray further stated that he believed if the tibiofibular ligaments were cut, that there would be enough broadening of the mortise to permit the same rotation as has been shown in the experiments and suggested that this experiment be made. **George E. Bennett, Baltimore, Md.**, described his method of using fascia to tie the ligaments in the operation for recurrent sprain. Bennett also suggested that when the foot is plantar flexed, a wider part of the astragalus comes in contact with the malleolus and this may tend to widen the mortise. He suggested that these experiments be done. **Isidore Cohn, New Orleans, La.**, regarded most sprains as fractures even if fragments are tiny, and suggested more thorough x-ray studies.

22. **Howard Mahorner, New Orleans, La.: Acute Hematogenous Osteomyelitis: A Study of 178 Cases.**—Following use of chemo- and immunotherapy in the past four years, mortality of acute osteomyelitis has been lowered from 24 to 6.6 per cent. Mahorner advocated conservative procedure consisting of hydration with electrolytes and blood transfusions, and chemo- and immunotherapy and minor operations only during early stages, delaying any major surgery until after better preparation of the patient and localization of the suppurative process. He felt strongly that a positive blood culture should be reversed before contemplating surgery. He noted osteoporosis to be the first x-ray evidence but seldom were positive findings seen before the eighth day. Necrosis of bone does not always occur even though the disease is extensive and sequestration frequently fails to appear roentgenologically or clinically.

Discussion: **Mims Gage, New Orleans, La.**, pointed out the two types of the disease, i.e., (1) profound systemic reaction with minor local symptoms, and (2) mild systemic reaction with intense local evidence of the disease. Operation in the first group, especially if the blood culture was positive, was followed by a mortality of over 50 per cent. He suggested novocain block of the sympathetics if evidence of vascular spasm existed, and also ligation of the femoral vein in certain cases. **Joseph E. J. King, New York, N. Y.**, requested information in regard to the incidence of metastasis following the use of the sulfonamides. **Lenox D. Baker, Durham, N. C.**, reviewed the four actions of the staphylococcus organism in regard to the symptomatology of osteomyelitis especially concerning toxemia. He advocated operation as soon as these factors could be properly dealt with and, also, staphylococcus antitoxin given intravenously with which he has had excellent results in acute hematogenous osteomyelitis with bacteremia. In closing, Mahorner stated that he found no reduction in metastases in his last group and also gave the advantages of adequate immobilization in all stages of the disease.

23. Harry J. Warthen, Richmond, Va.: **Gas Gangrene: An Analysis of Seventy-One Cases Treated in Civil Practice.**—In a study of all cases treated during the past 10 years an increasing mortality during the past 5 years was discovered. The disease was found to be more prevalent along the Eastern seaboard, and particularly so in Virginia. The recent increase in the mortality was thought to be due to the older age of the patients in this period, and possibly to increased and unjustified reliance upon chemotherapy to cure the disease without adequate surgery. Methods of treatment including chemo- and immunotherapy, x-ray, wide excision, and amputation were discussed and mortality figures given for each group (18.2 to 33.3 per cent).

Discussion: E. Dunbar Newell, Chattanooga, Tenn., considered pain at the site of the wound the most important symptom. He felt that early diagnosis could and should be made on clinical evidence alone without waiting for positive smears and x-rays. Howard M. Clute, Boston, Mass., had observed gas gangrene to follow abdominal operation in 3 cases with 2 recoveries. He considered early recognition the most important factor in the treatment, and this depends on the surgeon's acumen. Julian K. Quattlebaum, Savannah, Ga., described 3 fatal cases of gas gangrene that followed very minor injuries. Waller O. Bullock, Lexington, Ky., suggested the use of succinyl sulfathiazole for treatment. Warthen closed the discussion by presenting mortality figures following various methods of therapy. He observed a lower mortality following the average prophylactic dose of perfringens (26 per cent) than with the use of large doses (29 per cent).

24. John J. Morton, Rochester, N. Y.: **Inter-Innomino-Abdominal (Hind-quarter) Amputation.**—The high mortality accompanying this operation was cited by the author who reported the details of 4 personal cases. Only about 100 cases have been reported in the world literature. Two of the author's cases were done for sarcoma, one for metastasis from a thyroid carcinoma, and the other for chronic osteomyelitis. All of these patients recovered. Pictures and microphotographs of the specimens and x-rays were shown. The details of the operation were also discussed. Thomas C. Davison, Atlanta, Ga., reported such an operation performed for carcinoma in a patient aged 70 years, with a seven-year survival.

25. Frederic W. Bancroft, New York, N. Y.: **Improved Methods in Extremity Amputations for Diabetic Gangrene (abstract).**—The mortality figures of cases operated on by a sleeve type of thigh amputation were given, and then the improved statistics following a combination of the sleeve type of operation and refrigeration were cited. The changes were stimulated because of the extremely bad risk patient treated at the City Hospital and the mortality rate which under previous conditions had been prohibitive. In the sleeve operation as described by Fuller, the incision is made through the skin about the level of the tibial tubercle and carried directly through the fascia. The skin and fascia are then clipped together to prevent their separation—an important item to preserve the fascial blood supply. The tendons are transected as they pass through the popliteal space and the blood vessels are grasped and ligated. By scissor dissection the femur is separated from the surrounding bone, hugging the shaft in the dissection backwards. This prevents the opening of the various muscle bundles. The femur is cut through at the junction of the lower and middle third with a Gigli saw in order to prevent large bone chips being disseminated. The patella is then excised from the patellar tendon and the muscles allowed to drop back over the end of the femur. They can then be closed with interrupted layers for the fascia and for the skin without any tension. The technique of the refrigeration method consists of first applying ice at the level upon which a tourniquet is to be applied. This is usually figured to be about two inches above where the femur will be transected. A tourniquet is then



applied and the leg is packed in ice for at least two hours. It usually takes about 50 pounds of ice for a thigh amputation. The patient is transported to the operating room with the leg wrapped in ice and is only removed from the ice when everything is ready to perform the amputation. During the amputation all solutions used in irrigating the wound are to be cold. Thirteen operations were performed under this method, with two deaths, a mortality of 15.4 per cent. Bancroft stated that the skin temperature beneath the ice while refrigeration was being carried out was about 5 to 10° C. In cases with poor circulation the wound should be covered with ice bags for two or three days postoperative, in order to reduce the metabolism in the devitalized extremities. The two deaths that occurred in this series were probably due to emboli.

Discussion: W. F. Ruggiero, New York, N. Y., who was associated with the development of this method, stated that the tissues are not actually frozen. He was convinced that the infection so frequently associated with elderly diabetics was definitely inhibited, and as a consequence, lower amputations could be performed. M. S. Brown, New York, N. Y., who examined all of the patients, stated that the method allowed sufficient time to get such poor-risk patients in much better condition for major surgery. She observed no reactions following the use of the refrigeration method of anesthesia. Barney Brooks, Nashville, Tenn., observed experimental evidence that refrigeration preserved the vitality of tissues, but if associated with infection, the areas of necrosis become larger when normal temperatures return. Charles B. Venable, San Antonio, Texas, mentioned the advantages of performing a periarterial sympathectomy several days before amputation.

26. Leo Brady, Baltimore, Md.: *The Treatment of Trichomonas Vaginalis Vaginitis with the Lactobacillus.*—The results of another method of treatment of this condition were presented in which the lactobacillus was used. It was noted that this diagnosis was frequently missed because it either was not looked for or the examination was done at an unfavorable time. Stating that the trichomonas is the most frequent cause of leucorrhoea and finding that present treatment methods are not always successful, Brady set about to cure the condition by restoring the normal defense mechanism of the vaginal mucous membrane. Skimmed milk was inoculated with the lactobacillus vulgaris, then desiccated and divided into tablets, two of which were inserted into the vagina daily until the vaginal flora was restored to normal. Fifty patients treated in this manner obtained immediate relief, and there have been six recurrences. Samples from each lot of tablets used in this work were examined after being refrigerated for six months. At the end of this time each tablet was found to contain at least 10,000 viable lactobacilli.

27. W. C. Dixon, Nashville, Tenn.: *Post Vaginal Hernia (abstract).*—The condition usually but not always followed childbirth and was frequently associated with rectocele and uterine prolapse. It is, however, a definite entity with a peritoneal sac dissecting its way between the rectum and vagina, and was not to be confused with the deep sagging cul-de-sac of prolapse. Some congenital defect in the pelvic floor is probably of etiologic importance. The diagnosis was proved by examination with one finger in the rectum and one in the vagina. The treatment is operative—by abdominal section performing inversion and disposition of the sac and obliteration of the cul-de-sac by the Moschowitz technique. The vaginal approach is preferable unless other pathology requires the abdominal approach. This consists in opening the vaginal plate from the perineum to the cervix, dissecting the sac from the rectum and surrounding tissues, and ligating the neck of the sac with excision of the excess portion. The stump is then anchored behind the cervix and obliteration of the cul-de-sac is accomplished by approximating the uterosacral ligaments. A posterior colporrhaphy completes the operation. The details of a personal case were related.

28. Edward A. Kitlowski, Baltimore, Md.: **The Surgical Correction of Mandibular Prognathism.**—The removal of a section of the mandible on both sides for correction of prognathism was advocated and the reports of two cases were cited in which excellent results were obtained. In the first case the teeth were wired together, and in the second, the author used metal caps over the teeth. In this manner the patient was able to take food more quickly and just as satisfactory results were obtained.

29. J. Barrett Brown, St. Louis, Mo.: **Massive Repairs with Thick Split Skin Grafts.**—As far as could be told there is no relation between the blood group and the taking of skin grafts for homo-skin grafts and to the author's knowledge none of the grafts are ever permanent, but in numerous cases homo-skin grafts used as dressing have been lifesaving procedures in cases of extensive burns. Studies have been made with grouping donors into the M and N groups without changing this observation. The protection of and the healing of donor sites of skin grafts was discussed and the complete surface healing in six days by squamous epithelium from the follicles deep in the derma was shown microscopically.

30. Edward H. Richardson, Baltimore, Md.: **Diverticulum of the Ureter.**—The literature on diverticulum of the ureter was reviewed briefly. The first case was reported in 1911 and the first case demonstrated by intravenous pyelography was in 1936. A total of 32 clinical cases have been reported previously and in them, eight contained stones. As far as could be told from the cases reported, there was no characteristic syndrome. Richardson reported a case which is to his knowledge the largest one recorded to date. The patient was a female, aged 39, who complained of enlargement of the abdomen. There were absolutely no symptoms referable to the urinary system. At operation a large mass was found in the abdomen and from it was aspirated 3,500 c.c. of urine, and then the sac was removed and the ureter reconstructed. These diverticula may be either congenital or acquired.

31. Addison G. Brenizer, Charlotte, N. C.: **Ureteral Transplantation (abstract).**—A series of cases of ureteral transplantation and cystectomy done by the better known treatment methods was cited and compared with a series performed by the author's method. The efficacy of this procedure was proved by history, portrayal of the cases, and urograms made eight years after operation. A case was described in a male patient where the vasa deferentia and seminal vesicles had been preserved, a rim of bladder united over the prostatic urethra and a repair of the epispadias performed. Ejaculation and viable spermatozoa were maintained in a boy, 17 years of age, for eight years following operation. Another case cited was that of a girl 18 years of age, where the ureters and pelves were shown to have returned to approximately normal dimension in the course of eight years. A comparison of the author's method with the refinement of the original Coffey-Mayo procedure as done by Walter and Cabot, Ladd and Lanman, and Lower was outlined. It was pointed out that both operative methods had one very important point in common, i.e., they eventually turned the whole calibre of the ureter into the rectum and cut off the entire flow of urine to the bladder. The author's method required but one abdominal operation, whereas the Coffey-Mayo procedure required two. In his technique, the rectal mucosa was never opened nor transfixed with a suture and the abdomen never exposed to an infection from the bowel. The ureters were not cut immediately, but only after nine days, when they were embedded in the intestine after all hemorrhage, edema, and lameness had subsided. Brenizer further pointed out that his adaption of the incisions into the rectum loosely and the fact that the ureters were barely raised from their bed, did not disturb to any extent the blood supply and nerve supply to the ureter and allowed the ureter

to rotate in the intestinal channel. The intestine was able to better adapt itself to the ureter thus keeping it straight in its course in the intestine and causing no obstruction to it. His technique consisted of implanting simultaneously a segment of both intact ureters into the intestine within the mucosa. A long hairpin wire, sharpened on the ends, was made to straddle the ureter and to pierce the mucosa passing into a whistle tip catheter which had been placed in the rectum. The wire was passed through the catheter to emerge at the anus leaving a small loop surrounding the ureter. Eight days later the ureter was enveloped by the wire loop and implanted into the intestine, and then severed by the application of an electrocutting current to the wire ends emerging through the catheter at the anus. The assurance that each ureter was severed and totally turned into the rectum was easily ascertained by the absence of flow of urine into the bladder and the flow of urine into the rectum, proved by urograms.

**32 Lawrence R. Wharton, Baltimore, Md. Simultaneous Obstruction of Both Ureters with Uremia (abstract).**—The author presents a series of 7 cases of simultaneous obstruction of both ureters with uremia. The causes were stricture, 2 cases; stone, 2 cases; carcinoma of bladder, 1 case; back pressure from over distended bladder, 1 case; bilateral ligation of ureters, 1 case. The commonest causes are stricture and stone, both of which are often associated with infection. In all of these cases there had been urinary disease for years before acute obstruction with uremia developed. But in all these cases of stricture and stone, the situation had been neglected by the patient because it was causing no pain, or was treated observantly by the physician. These cases show that serious urinary disease may be present without causing any pain. Typical ureteral colic may be absent in ureteral obstruction. Urinary infection, incomplete obstruction and stone should not be neglected or allowed to progress to complete renal destruction. There was one fatality in this series, due to carcinoma of the bladder. The author discussed methods of treatment and problems that arise during treatment of various types of ureteral obstruction.

**Discussion.** W. H. Parsons, Vicksburg, Miss., stated that he still used the multiple stage operation and in his hands it is better and has a much lower mortality and morbidity. H. L. Foss, Danville, Pa., made a plea for a return to the simple forms of transplantation, the use of nonabsorbable sutures, and the use of sulfonamide drugs. He reported 5 cases seen in the past few weeks on which he had obtained excellent results.

**33 Ambrose H. Storek, New Orleans, La. The Use of Estrogenic Substances in the Preoperative and Postoperative Treatment of Hyperthyroidism. Further Observations (abstract).**—Various possible mechanisms which might account for the experimentally observed lowering of basal metabolism which follows the administration of estrogenic substances and which might account for the beneficial effects following the administration of estrogenic substances to patients with hyperthyroidism were discussed. The group included the suggestion by Sherwood, and later by Grumbrecht and Loesser, that estrogen may inhibit the production of anterior pituitary thyrotropic hormone; the possibility of a direct hormone antagonism in the tissues, as later suggested by Sherwood in view of his demonstration that estrogen therapy causes lowering of basal even in thyroidectomized animals, and inhibitions of production of various anterior pituitary calorigenic hormones. Observations made in 11 cases with hyperthyroidism in which the usual supplementary treatment including bed rest, sedation, and the administration of iodine, calcium, vitamins and a high caloric, high protein diet was supplemented with estrogen therapy, using either theelin in oil or diethyl stilbestrol given by mouth, were summarized and compared with a series of control cases who received the same basic treatment but to whom estrogenic substances were not given. Even in cases refractory to the usual preoperative

treatment, an additional lowering of basal metabolic rate followed estrogen therapy. An average preoperative lowering of pulse rate equal to that which occurred in the control group was observed in the estrogen treated cases, even though more of the cases which received estrogen therapy were iodine fast at the time of admission. The average peak pulse rate on the first postoperative day in the cases which received estrogen therapy was lower than was the average peak pulse rate on the same day in the control group. Patients who received estrogens consistently looked and felt better than did the control group, this difference being most pronounced during the immediate postoperative period. Although no definite conclusions can so far be drawn concerning a relation between dosage and effect, comparison of the presently reported observations with those following smaller average doses suggests that small doses of estrogenic substances are equally, if not more effective, than are large doses. Reference was made to the possibility of refractoriness to estrogen therapy following repeated doses. Estrogen therapy is probably most effective when administered for from four to seven days preceding operation when subtotal thyroidectomy is done in one stage. When multiple stage thyroidectomy is performed, it seems advisable to continue estrogen therapy for several days following the first stage, and if there is a lapse of more than a week between operations, to reinstitute estrogen therapy preceding the second stage. It was believed that the employment of this form of collateral therapy is valuable in severe hyperthyroidism, particularly when multiple stage procedures are necessary, and in iodine fast cases. No conclusions can yet be drawn concerning the relative values of theelin and diethylstilbestrol as estrogenic substances suitable for use in hyperthyroidism.

41 Edward T. Newell, Chattanooga, Tenn. **The Treatment of Cancer of the Breast Using Caustery Excision, Implantation of Radium, Preoperative and Postoperative, Radiation** (abstract).—The author reviewed his experiences and divided the cases into (1) inoperable, (2) operable confined within its limits, and (3) operable with metastases. By reason of the fact that the Halsted operation or the Wills Meyer operation produced only 25 per cent of cures where axillary involvement was present, Newell was of the opinion for many years that something in addition to the perfect radical operation should be done to increase this low 5 year arrest and it was for that reason that he instituted the use of radium in the axilla and postoperative x-ray treatment. He believes that this has increased the number of 5 year cures (arrest) at least 10 per cent with the addition of the caustery resection and postoperative irradiation. In rare instances preoperative irradiation was used. In comparison, twice as many patients lived three or more years without axillary or other metastases as did those with such extension (51 vs. 10.6 per cent). In a series of 60 personal cases he found that Grade 3 and 4 predominated (70 per cent), and there was an operative mortality of 4 per cent. The details of the author's method of using caustery excision and radium implantation were shown by a motion picture. Average duration of the tumor was 17.5 months, and 68.6 per cent had axillary metastases. He used preoperative radiation only in the well advanced cases and followed in 4 to 5 days with the surgical attack.

Discussion. Hugh A. Gumble, Greenville, Miss., used the caustery method of excision. He also advocated transplantation of the latissimus dorsi over the denuded chest and axilla. No swelling in the area followed this method. Deryl Hart, Durham, N. C., raised the question of increased swelling of the area following implantation of radium and caustery excision. He described the methods used at Duke Hospital stressing the advantage of a light plaster cast dressing to promote primary wound healing. Bradley L. Coley, New York, N. Y. talked about the disadvantages of preoperative x-ray treatment mentioning particularly the skin changes and scar formation. He stated that postoperative radia-

tion was used at Memorial Hospital and described the operative technique used there. In his opinion inflammatory carcinoma was inoperable. John E. Cannaday, Charleston, W. Va., pointed out the value of getting patients out of bed early, and also advocated the use of cotton suture material.

35. D. Henry Poer, Atlanta, Ga.: **Effect of Removal of Malignant Thymic Tumor in a Case of Myasthenia Gravis** (abstract).—Statistical evidence was given to show the presence of thymic abnormalities in over 50 per cent of cases of myasthenia gravis as proved by autopsy or operation. The increase in this percentage in recent years indicates the probability of a consistent association of these conditions. The extraordinarily few operations that have been performed upon patients with myasthenia gravis have usually been done for removal of benign thymic tumors, and the results were not particularly encouraging. Recently Blalock and his associates have removed a thymic cyst from a patient, which was followed by dramatic improvement, and they also have explored the thymic area of six myasthenic patients removing remnants from all with encouraging beneficial results. In the literature only four reports of malignant thymic tumor could be found that have been discovered at autopsy in cases of myasthenia gravis. The author adds a report of a carcinoma of the thymus which was successfully removed from a 52-year-old male who had suffered with a severe form of myasthenia gravis for 2 years. This was followed by marked clinical improvement and no evidence of recurrence up to the present time.

Discussion: Joseph E. J. King, New York, N. Y., mentioned the 2 cases operated upon by Campbell and asked if they had been included in the cases studied. Edward D. Churchill, Boston, Mass., pointed out the difficulty of establishing a definite diagnosis of myasthenia gravis. He gave his experience in dealing with four patients with mediastinal tumors who at one time or another presented symptoms suggestive of myasthenia gravis. He considered the response to prostigmin to be the most accurate diagnostic test (described by Viets). Barney Brooks, Nashville, Tenn., stated that he had recently examined Blalock's first patient (thymic cyst removed in 1936) and found no symptoms of myasthenia gravis.

36. Daniel L. Borden, Washington, D. C.: **Personal Observations During the Recent A. M. A. Trial**. The details and many personal incidents of the recent trial of the American Medical Association were described. This was discussed by John H. Lyons and Harry H. Kerr, Washington, D. C., who related the involvement of the local Medical Society in this important trial.

37. Amos R. Koontz, Baltimore, Md.: **Are Selective Service Rejections an Index of the State of Our National Health?**—It was pointed out that many misstatements concerning this question are receiving popular attention at the present time. The statement that 40 per cent of our draftees are undernourished was found to be grossly untrue. Koontz stated that the average height is the same, the average weight is better, and the number of rejections for tuberculosis is less than in World War I. He found venereal diseases decreasing in the Army in spite of recent statements to the contrary, and that bad teeth were the principal cause for rejection. He also noted a much lower morbidity and mortality rate than in World War I and that the general health and morale were good.

Discussion: Harvey B. Stone, Baltimore, Md., emphasized the bad effects on the public morale of the absurd misstatements that have received so much publicity. He had found public health in relatively good condition.

# Book Reviews

---

**Surgical Diseases of the Spinal Cord Membranes and Its Roots.** By Charles A. Elsberg. Pp. 598, with 249 illustrations. New York City, 1941, Paul B. Hoeber, Inc. \$14.00.

This is a new and revised edition of the author's previous books on the spinal cord, *Diseases of the Spinal Cord*, 1916, and *Tumors of the Spinal Cord*, 1925. Chapter III, The Roentgen Ray Diagnosis of the Spinal Cord Meninges and Vertebrae, was written by Cornelius G. Dyke and Chapter VIII on the pathology of cord tumors was written by Abner Wolf.

It is an excellent monograph reflecting the author's extensive experience, his multiple contributions on the spinal cord which have been published in the periodical literature since 1912, and a thorough knowledge of the literature. Positive statements are made concerning the author's opinion and practice even on the most controversial subjects.

The illustrations, 249 in number, are well chosen and well reproduced. Chapter subdivisions in large type and the free use of italicized paragraph headings for lesser subdivisions make the book more readable. At the end of the book, references are listed alphabetically and there is also a list of authors with page references to each. However, not all references are listed and the page references to authors listed are also incomplete. These omissions are noted especially in Chapter VIII.

In general the style is clear and the diction good. But on page 185 it is stated that "the primary lesion was metastatic." One who has recently learned anatomy would ponder on the location referred to as follows "on the lower part of the cheek below the area of distribution of the inframaxillary part of the trigeminus" (Page 790).

Many surgeons would disagree with the statement that "the region from which a foreign body has been removed should be gently swabbed with weak iodine so as to forestall a possible secondary infection."

This book is favorably recommended to everyone who examines or treats surgical diseases of the spinal cord.

---

## Books Received

The receipt of books is acknowledged in this section and this statement must be regarded as sufficient acknowledgment of the courtesy of the senders. Selections will be made for more extensive review dictated by the interests of our readers and as space permits.

**OPERATIVE SURGERY • ABDOMINAL SURGERY** By F. W. Bancroft, A.B., M.D., F.A.C.S., Associate Clinical Professor of Surgery, Columbia University, New York City. Cloth. Pp. 1102, with 270 illustrations. New York, 1941, D. Appleton Century Co., Inc.

**SULFANILAMIDE AND RELATED COMPOUNDS IN GENERAL PRACTICE** By Wesley W. Spunk, M.D., Associate Professor of Medicine, University of Minnesota. Cloth. Price \$1.00. Pp. 256. Chicago, 1941, The Year Book Publishers, Inc.

**TEXTBOOK OF GENERAL SURGERY.** By Warren H. Cole, M.D., F.A.C.S.; and Robert E. Egan, M.D., Department of Surgery, University of Illinois, Chicago. Cloth. Price \$5.00. Pp. 1067, with 578 illustrations. New York, 1941, D. Appleton Century Co., Inc.

**WOUNDS AND FRACTURES: A CLINICAL GUIDE TO CIVIL AND MILITARY PRACTICE.** By H. Winnett Orr, M.D., F.A.C.S., Nebraska Orthopedic Hospital. Cloth. Price \$5.00. Pp. 227, with 137 illustrations. Springfield, Ill., 1941, Charles C Thomas, Publisher.

**DISEASES OF THE THYROID GLAND.** By Arthur E. Hertzler, M.D. Cloth. Price \$8.50. Pp. 670, with 495 illustrations. New York, 1941, Paul B. Hoeber, Inc.

**A MANUAL OF THE TREATMENT OF FRACTURES.** By John A. Caldwell, M.D., Professor of Clinical Surgery, University of Cincinnati College of Medicine. Cloth. Price \$3.50. Pp. 150, with 76 illustrations. Springfield, Ill., 1941. Charles C Thomas, Publisher.

**TREATMENT OF THE PATIENT PAST FIFTY.** By Ernst P. Boas, M.D., Associate Physician, Mount Sinai Hospital, New York City. Cloth. Price \$4.00. Pp. 324, with 19 illustrations. Chicago, 1941, The Year Book Publishers, Inc.

**SURGERY OF THE HEART.** By E. S. J. King, M.D., M.S., D.Sc., F.R.C.S. (Eng.), F.R.A.C.S., Major A.A.M.C., University of Melbourne, Australia. Cloth. Price \$13.50. Pp. 728, with 268 illustrations. Baltimore, 1941, Williams and Wilkins Co.

**EPILEPSY AND CEREBRAL LOCALIZATION.** By Wilder Penfield, Litt.B., M.D., D.Sc., McGill University, Montreal; and Theodore C. Erickson, M.A., M.Sc., M.D., McGill University, Montreal. Cloth. Price \$8.00. Pp. 623, with 163 illustrations. Springfield, Ill., 1941, Charles C Thomas, Publisher.

**SURGICAL CLINICS OF NORTH AMERICA.** By nineteen contributors. Cloth. Pp. 1521, with 348 illustrations. Philadelphia, 1941, W. B. Saunders Co.

**SURGICAL PRACTICE OF THE LAHEY CLINIC.** By Frank H. Lahey, M.D., and others. Cloth. Pp. 897, with 376 illustrations. Philadelphia, 1941, W. B. Saunders Co.

**SURGICAL CLINICS OF NORTH AMERICA.** By many contributors. Cloth. Pp. 333, with 389 illustrations. Philadelphia, 1941, W. B. Saunders Co.

**SURGERY OF MODERN WARFARE.** By Hamilton Bailey, F.R.C.S., Royal Northern Hospital, London. Cloth. Price \$10.00. Pp. 899, with 828 illustrations. Baltimore, 1941, Williams and Wilkins Co.

**ENDOTRACHEAL ANESTHESIA.** By Noel A. Gillespie, M.D., State of Wisconsin General Hospital, Madison, Wisconsin. Price \$4.00. Pp. 187, with 44 illustrations. University of Wisconsin, 1941, University of Wisconsin Press.

**PSYCHOSURGERY: INTELLIGENCE, EMOTION AND SOCIAL BEHAVIOR FOLLOWING PREFRONTAL LOBOTOMY FOR MENTAL DISORDERS.** By Walter Freeman, M.D., Ph.D., F.A.C.P.; James W. Watts, B.S., M.D., F.A.C.S., George Washington University, Washington, D. C. Cloth. Price \$6.00. Pp. 337, with 81 illustrations. Springfield, Ill., 1942, Charles C Thomas, Publisher.

**A TEXT BOOK OF NEURO-ANATOMY, ed. 3.** By Albert Knutz, Ph.D., M.D., Professor of Micro-Anatomy, St. Louis University School of Medicine. Cloth. Price \$6.00. Pp. 518, with 207 illustrations. Philadelphia, 1942, Lea and Febiger.

**CLINICAL ROENTGENOLOGY OF PREGNANCY.** By William Snow, M.D., Director of Radiology, Bronx Hospital. Cloth. Price \$4.50. Pp. 178, with 117 illustrations. Springfield, Ill., 1942. Charles C Thomas, Publisher.

**HELP YOUR DOCTOR HELP YOU (SERIES):** (1) Colitis (2) Food Allergy (3) Gallstones and Diseases of the Gallbladder (4) Gastric or Duodenal Ulcer (5) Migraine. Editorial Board, Dr. Walter C. Alvarez, Editor-in-Chief. New York, 1941, Harper & Brothers.

# SURGERY

VOL. 11

MAY, 1942

No. 5

## Original Communications

### THE LOCAL IMPLANTATION OF SULFANILAMIDE IN THE PERITONEAL CAVITY AND ITS CLINICAL APPLICATION IN PERITONITIS

K. TASHIRO, M.D., PH.D., O. B. PRATT, M.D., N. KOBAYASHI, M.D., AND G. K. KAWAICHI, M.D., LOS ANGELES, CALIF.

FEW eras in the history of man have been as productive of far-reaching radical changes in the way of life as the present. We have seen pre-eminently two startling developments, which, as medical men and as human beings, have impressed us because of the very opposite-ness of their implications. One is the development of sulfanilamide with its unheralded powers of salvation in man's fight against suffering and death, and the other is the revolution of established military concepts and the perfection of new technique in the art of killing men—war.

Despite the constant refinement of surgical technique, numerous ingenious devices, mechanical and medical, to decompress the patient, improvement of pre- and postoperative care, the cryptic admission must still be made—too many patients die of peritonitis. The mortality of peritonitis from appendicitis alone is appalling, viewed from the standpoint of surgeon, statistician, or layman. Perhaps the most significant work to appear in recent years on the treatment of peritonitis associated with appendicitis is that of Ravdin, Rhoads, and Lockwood.<sup>1</sup> In a series of 809 consecutive cases of acute appendicitis, they were able to reduce the mortality from 1.5 per cent in the first 552 cases to 0.4 per cent in the last 257 cases. They attributed this marked improvement to the employment of sulfanilamide, orally and parenterally, in all severe cases of the latter group, no other factor being changed.

Originally deemed a specific for infections due to the beta-hemolytic streptococcus the impression was not easily shaken, and the earlier use of prontosil and its derivatives was quite restricted. It is very interesting to note, however, that the first recorded clinical report on the use of prontosil appeared in 1933, a case of staphylococcus septicemia successfully treated in a child 10 months of age.<sup>2</sup> Thus the history of

Received for publication, June 30, 1941.



the prontosil as well as its allied chemotherapeutic derivatives is one of apparent contradictions. We have seen how sulfanilamide, originally labeled for beta-hemolytic streptococcus, has successfully combated many infections, among others those due to gonococcus, pneumococcus, brucella, colon bacillus and Ducrey's bacillus.

Although the mode of action of sulfanilamide is not yet clearly understood, it has been hitherto shown that to be effective sulfanilamide must gain contact with the invading organism, and this is usually by means of the circulating blood. Colebrook and his co-workers and Long and Bliss have shown that sulfanilamide possesses bacteriostatic properties in dilutions as great as 1:10,000 and higher.<sup>3</sup> Yet no tissue damage had been demonstrated in parenteral and intrathecal injections in solutions of 1 per cent. These foregoing facts and also consideration of sulfanilamide's apparent disregard for specific labels led us independently early in 1939 to implant sulfanilamide powder, later crystals, in all traumatic wounds that were infected or that had potentiality of infection—cuts, lacerations, abrasions. We reasoned, perhaps naively, that if this peculiar drug's effectiveness at a given site depended upon being circuitously carried there by the blood after absorption via the gastrointestinal tract, why could not we, under favorable conditions, put it there in the first place? Thus empirically used, the results were highly gratifying; we saw no evidence of tissue irritation; most infected wounds healed quickly, and potentially infected cuts healed per primam after suture. These results were certainly contrary to what should be expected in the light of the current opinion based on studies *in vitro*. Long and Bliss<sup>3</sup> and others denied the possible efficacy of sulfanilamide applied locally.

In July, 1939, appeared the highly significant work of Jensen, Johnsrud, and Nelson on the direct implantation of sulfanilamide into compound fracture wounds.<sup>4</sup> Thirty-nine cases were presented, including 2 compound dislocations, all contaminated, all débrided, all closed and healed per primam. Our next anticipated venture was the implantation of sulfanilamide directly into the peritoneal cavity in peritonitis, and opportunity came on Dec. 16, 1939, in the form of a ruptured pelvic appendix with peritonitis, the case report of which is later presented (Case 1).

In this report we present our experiences with sulfanilamide implanted directly into the abdomen in cases of peritonitis and appendiceal abscesses as encountered in a private practice. Also is included a clinical study of sulfanilamide blood levels in these patients following intraperitoneal implantation, and collateral experimental studies using the rabbit. The laboratory animals were used to compare the drug's blood concentration with intra-abdominal concentration at time intervals, and to examine the peritoneal tissues microscopically for possible pathologic changes.

## ILLUSTRATIVE CLINICAL CASES

CASE 1.—M. T., a boy, 15 years of age, entered the hospital Dec. 16, 1939, with history of stomach-ache of three days' duration. On the day previous to entry, he had taken castor oil and a painful bowel movement followed. At 3:30 P.M. on the day of entry, he suffered a sudden severe lower abdominal pain, followed by nausea and vomiting, after which the pain remained constant and severe, and his "stomach stayed hard." Physical examination revealed a well-developed boy with temperature, 100°; pulse, 118; respiration, 20; blood pressure, 118/60. Examination of heart and lungs was negative. The abdomen was held rigid with maximum tenderness in the suprapubic region; rebound tenderness was present. Rectal examination showed definite tenderness to the right. A diagnosis of ruptured pelvic appendicitis was made.

Appendectomy was performed under spinal anesthesia about three and one-half hours after approximate time of rupture. A perforated pelvic appendix was found with pelvic pus accumulation. The appendix was removed and the pelvic peritoneal cavity lavaged with about 500 c.c. of normal saline solution. One gram of sulfanilamide crystals was placed in the appendix bed, and the abdomen closed, using 0.5 Gm. sulfanilamide in the wound. A small Penrose drain was inserted. The temperature dropped to normal on the second postoperative day. Recovery was uneventful and the patient walked from the hospital on the ninth postoperative day.

This was the first case in which we used sulfanilamide crystals intraperitoneally, hence the trial dose was one gram, and a drain was placed. Nevertheless, in the light of previous tedious experiences with similar cases of pelvic peritonitis, we were quite elated with the results, and the incentive to enlarge our experience was stimulated.

CASE 4.—A. I., male, 20 years of age, entered the hospital April 13, 1940, with history of stomach-ache since that morning, five hours later a lower abdominal pain with a desire to defecate, then a sudden severe pain in the lower midabdomen followed by nausea and vomiting. Physical examination revealed temperature, 104°; pulse, 118; respiration, 20; blood pressure 115/50. Examination of the heart and lungs was negative. The abdomen was tender in the right lower quadrant and suprapubic region with definite rebound tenderness. Urinalysis showed occasional pus cell and occasional *B. coli*. A diagnosis of ruptured pelvic appendicitis was made.

Appendectomy was performed under spinal anesthesia, and a perforated appendix was found in the pelvis. The pelvic peritoneal cavity was lavaged with warm normal saline solution, and 8 Gm. of sulfanilamide were placed in the pelvis. One gram was distributed in the wound and the abdomen closed without drains. Pus culture from the appendix was reported *B. coli*. The temperature was normal on the first postoperative day but began to rise on the second. Sulfanilamide was given orally 25-50 with sodium bicarbonate t.i.d. The temperature again dropped to normal after one day, but oral sulfanilamide was continued for three days. The patient made an uneventful recovery and left the hospital ambulatory on the seventh postoperative day.

CASE 11.—Y. N., a man, 65 years of age, entered the hospital on July 27, 1940, with abdominal pain after exerting upper abdominal pain of sudden onset four hours previous to entry. A diagnosis of carcinoma of stomach with partial obstruction had been made the previous week, refusing operation, the patient had been discharged just five days before. Physical examination revealed a patient resting quietly with the effects of adequate opiates. Temperature, 98.4°; pulse, 64;

respiration, 20; blood pressure, 95/65. The heart and lungs were negative. The abdomen showed marked rigidity, general tenderness to pressure, marked rebound tenderness, obliteration of liver dullness to percussion. Urinalysis negative for sugar and albumin, microscopically a few fine granular casts present. R.B.C., 4,480,000; Hgb., 96 per cent Sahli; W.B.C., 6,000; polymorphonuclears, 86 per cent. Diagnosis: Carcinoma of the stomach ruptured, with peritonitis.

Operation was performed under high spinal anesthesia five hours after rupture. On opening the peritoneal cavity through an upper middle incision, escape of gas was noted, peritoneal surfaces inflamed, abdomen soiled by partially digested rice and vegetables with high odor of vomitus. Perforation of about 1 cm. was found on anterior wall at lesser curvature just proximal to pyloric ring, food particles, bubbles, and liquid matter still issuing. The tumor mass around the perforation was about the size of a small egg, hard, firmly adherent, and infiltrating pancreatic tissue. Lesser sac was also filled with stomach content. Subtotal gastric resection and antecolic gastroenterostomy performed, mobilization of the pyloric end required adequate removal of involved pancreatic tissue. One bean-sized indurated subpyloric gland was removed, with no further evidence of metastasis. Peritoneal cavity was thoroughly lavaged clean of an immense amount of debris. Eight grams of sulfanilamide were implanted circa anastomosis and center of soilage, two grams in wound layers. The abdomen was closed without drainage. Seven grams sulfanilamide were given by hypodermoclysis on the first two postoperative days. Daily blood and urine examinations showed no significant changes. Although this patient had a febrile postoperative course, due chiefly to bronchopneumonia, there were no intra-abdominal complications. On the eighth postoperative day, during a cough seizure, the lower two inches of the wound gave way and he eviscerated about three feet of small intestine. The bowel loops were washed with normal saline solution, coated with 4 Gm. of sulfanilamide, returned to the abdomen, and the wound repaired. There were still no abdominal complications, no wound infection.

CASE 12.—M. F., male, aged 21, taken to hospital August 17, 1940, with severe lower abdominal pain since early morning, unrelieved by morphine. History of midabdominal pain five days before gradually increasing in severity with localization below navel day before entry. Had three watery bowel movements on the same day with no urinary symptoms. Physical examination revealed a patient, quite toxic, moaning and restless with pain, thighs flexed on abdomen. Temperature, 98.6°; pulse, 68; blood pressure, 120/70. Examination of heart and lungs was negative. Abdomen flat, showing generalized rigidity and tenderness, maximal tenderness and rigidity in lower right quadrant. No audible peristalsis. Urine negative for albumin, sugar, and sediment. Hgb., 110 per cent Sahli; W.B.C., 24,100 with 88 per cent polymorphonuclears. Diagnosis: ruptured appendix.

Operation was performed under spinal anesthesia; purulent fluid noted immediately on opening the peritoneum. Exactly 100 c.c. thick, purulent material aspirated from the pelvis. A large appendix covered with plastic exudate, containing two large fecal stones, and bearing two perforations was removed from a low retrocecal position. The pelvic cavity and appendix "bed" were thoroughly lavaged with warm normal saline solution. Ten grams sulfanilamide crystals were distributed in the pelvis and the appendix bed, and the closure was without drainage, using one gram sulfanilamide in the wound layers. From the second to sixth postoperative day, sulfanilamide was given orally, 10 gr. t.i.d. with soda bicarbonate. Temperature reached normal on the fourth postoperative day and rose to 99.2° on the fifth, due to wound hematoma. The patient was discharged ambulatory on the seventh day.

The sulfanilamide we employed was stocked in glass ampoules in crystalline form by the Abbott Laboratories. Beyond receiving assur-

ance of its sterility by private communication with the manufacturers no further bacteriologic studies were made. The crystals were transferred to a sterile dry cup and poured directly into the abdominal cavity.

In recapitulation, given an adequately prepared patient, our operative technique is essentially as follows:

1. Spinal anesthesia is the anesthesia of choice; ether or local novocain is used as indication demands.

2. The abdomen is opened through any incision appropriate to the condition, but the McBurney is the incision of choice in our appendectomies.

3. The field is isolated with moist gauze packs, and the abdominal wound protected with towels. Lately we have been using waterproof cellophane incorporated between gauze layers for wound protection, and we believe wound infections have been further decreased.

4. Thorough aspiration of pus and infective material from the abdomen is stressed; all possible gangrenous tissue is removed; and further, the regional abdomen is cleansed by repeated perfusion with warm normal saline solution and suction.

5. Crystalline sulfanilamide in amounts of 4 to 10 Gm., depending on the patient's age, is implanted directly in the area of greatest infection, with 2 to 3 Gm., governed by the size of the incision, used to coat wound layers and surfaces before closure.

6. Pus per se is no indication for drainage. Drains are limited to instances in which irremovable gangrenous tissue or tissue of doubtful viability must be left behind at closure.

7. Supplemental sulfanilamide therapy is continued orally after the first postoperative day. After surgical procedures involving anastomosis of hollow viscera, and in patients unable to take oral medication, the sulfanilamide is given parenterally.

#### EXPERIMENTAL FINDINGS

In December, 1939, we arbitrarily placed one gram of sulfanilamide into the pelvic peritoneal cavity of a patient with peritonitis from a ruptured pelvic appendix. Jensen and co-workers<sup>4</sup> had shown that 5 to 15 Gm. could be safely implanted in compound fracture wounds and closed. In the succeeding three cases we, therefore, felt safe in employing doses of 8 to 10 Gm. The results were encouraging, but the dosage was still quite arbitrary. At this point, to establish some rational basis for further work, we enlisted the technical assistance of our coauthor, Dr. O. B. Pratt, and the facilities of the White Memorial Hospital Laboratory.

#### METHOD

In the present investigation, white rabbits weighing an average of four pounds were used. Under ether anesthesia, the peritoneal cavity was opened and sulfanilamide crystals implanted, ranging in amounts

respiration, 20; blood pressure, 95/65. The heart and lungs were negative. The abdomen showed marked rigidity, general tenderness to pressure, marked rebound tenderness, obliteration of liver dullness to percussion. Urinalysis negative for sugar and albumin, microscopically a few fine granular casts present. R.B.C., 4,480,000; Hgb., 96 per cent Sahli; W.B.C., 6,000; polymorphonuclears, 86 per cent. Diagnosis: Carcinoma of the stomach ruptured, with peritonitis.

Operation was performed under high spinal anesthesia five hours after rupture. On opening the peritoneal cavity through an upper middle incision, escape of gas was noted, peritoneal surfaces inflamed, abdomen soiled by partially digested rice and vegetables with high odor of vomitus. Perforation of about 1 cm. was found on anterior wall at lesser curvature just proximal to pyloric ring, food particles, bubbles, and liquid matter still issuing. The tumor mass around the perforation was about the size of a small egg, hard, firmly adherent, and infiltrating pancreatic tissue. Lesser sac was also filled with stomach content. Subtotal gastric resection and antecolic gastroenterostomy performed, mobilization of the pyloric end required adequate removal of involved pancreatic tissue. One bean-sized indurated subpyloric gland was removed, with no further evidence of metastasis. Peritoneal cavity was thoroughly lavaged clean of an immense amount of debris. Eight grams of sulfanilamide were implanted circa anastomosis and center of soilage, two grams in wound layers. The abdomen was closed without drainage. Seven grams sulfanilamide were given by hypodermoclysis on the first two postoperative days. Daily blood and urine examinations showed no significant changes. Although this patient had a febrile postoperative course, due chiefly to bronchopneumonia, there were no intra-abdominal complications. On the eighth postoperative day, during a cough seizure, the lower two inches of the wound gave way and he eviscerated about three feet of small intestine. The bowel loops were washed with normal saline solution, coated with 4 Gm. of sulfanilamide, returned to the abdomen, and the wound repaired. There were still no abdominal complications, no wound infection.

CASE 12.—M. F., male, aged 21, taken to hospital August 17, 1940, with severe lower abdominal pain since early morning, unrelieved by morphine. History of midabdominal pain five days before gradually increasing in severity with localization below navel day before entry. Had three watery bowel movements on the same day with no urinary symptoms. Physical examination revealed a patient, quite toxic, moaning and restless with pain, thighs flexed on abdomen. Temperature, 98.6°; pulse, 68; blood pressure, 120/70. Examination of heart and lungs was negative. Abdomen flat, showing generalized rigidity and tenderness, maximal tenderness and rigidity in lower right quadrant. No audible peristalsis. Urine negative for albumin, sugar, and sediment. Hgb., 110 per cent Sahli; W.B.C., 24,400 with 88 per cent polymorphonuclears. Diagnosis: ruptured appendix.

Operation was performed under spinal anesthesia; purulent fluid noted immediately on opening the peritoneum. Exactly 100 c.c. thick, purulent material aspirated from the pelvis. A large appendix covered with plastic exudate, containing two large fecal stones, and bearing two perforations was removed from a low retrocecal position. The pelvic cavity and appendix "bed" were thoroughly lavaged with warm normal saline solution. Ten grams sulfanilamide crystals were distributed in the pelvis and the appendix bed, and the closure was without drainage, using one gram sulfanilamide in the wound layers. From the second to sixth postoperative day, sulfanilamide was given orally, 10 gr. t.i.d. with soda bicarbonate. Temperature reached normal on the fourth postoperative day and rose to 99.2° on the fifth, due to wound hematoma. The patient was discharged ambulatory on the seventh day.

The sulfanilamide we employed was stocked in glass ampoules in crystalline form by the Abbott Laboratories. Beyond receiving assur-

The blood concentration was determined in each case and compared with the coincident intraperitoneal concentration; this local concentration was determined by rinsing the peritoneal cavity with 150 c.c. of sterile water to recover the dissolved sulfanilamide.

The other portion of our investigation dealt with the determination of blood sulfanilamide levels in patients after known quantities of sulfanilamide were implanted intraperitoneally and the abdomen closed without drainage.

### RESULTS

Fig. 1 shows that the average maximum concentration in the blood was 22 mg. per 100 c.c. in rabbits that received one gram intraperitoneally.

Rabbits that received 2 Gm. of sulfanilamide had a maximum blood concentration of 57 mg. per 100 c.c. but died in thirty-six hours. Rabbits that received 15 Gm. had a maximum blood concentration of 270 mg. per 100 c.c. and died in fifteen hours.

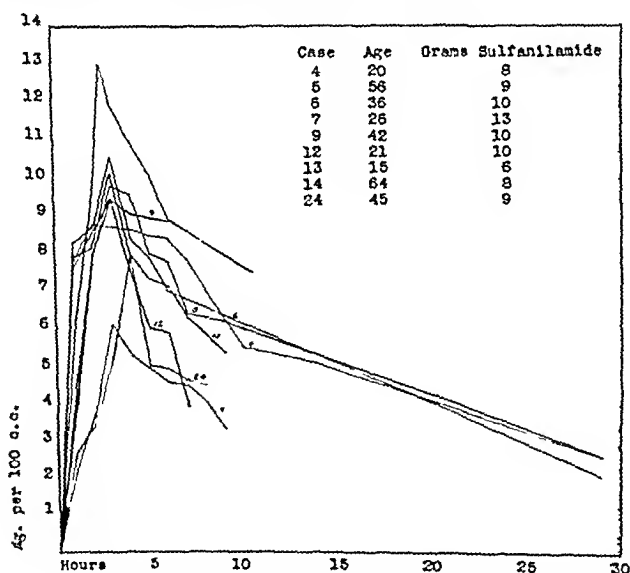


Fig. 3. Hourly blood sulfanilamide levels in patients receiving known quantities of sulfanilamide intraperitoneally at operation.

Fig. 2. It is seen that there was a rapid fall in the intraperitoneal concentration as the blood concentration increased. At about six hours the sulfanilamide concentration in the blood about equaled the concentration in the peritoneal cavity, after which the blood concentration exceeded the peritoneal concentration.

Fig. 1. Concentration curves were plotted for patients receiving known amounts of sulfanilamide intraperitoneally at operation. In Case 4, nine grams were used and the blood concentration rose to 9 mg.; Case 5, nine grams showed a rise to 9.8 mg.; Case 6, ten grams showed

from 1 to 15 Gm. In four rabbits one gram was used (Fig. 1). Blood was taken from the heart at hourly intervals and the concentration of sulfanilamide determined. Microscopic sections were made of the intestines and the peritoneum at intervals to search for any possible pathologic changes.

In another series of ten rabbits, one gram of sulfanilamide was placed intraperitoneally and the rabbits sacrificed at hourly intervals (Fig. 2).

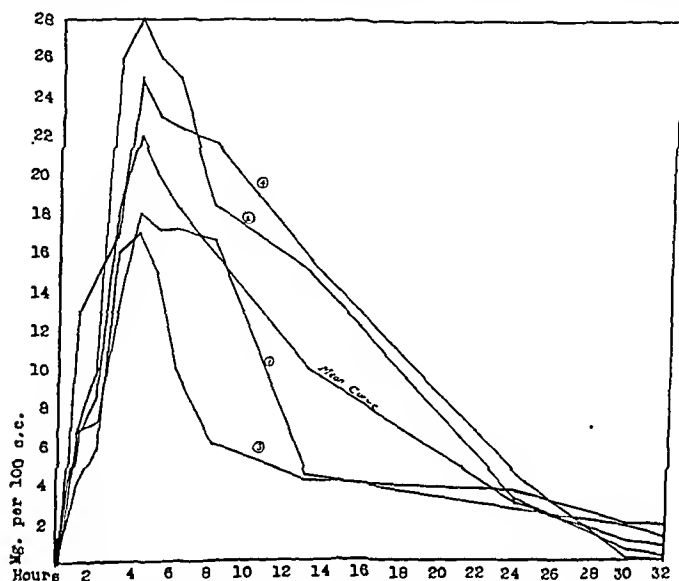


Fig. 1.—Hourly blood sulfanilamide levels in rabbits receiving 1 gram of crystalline sulfanilamide intraperitoneally.

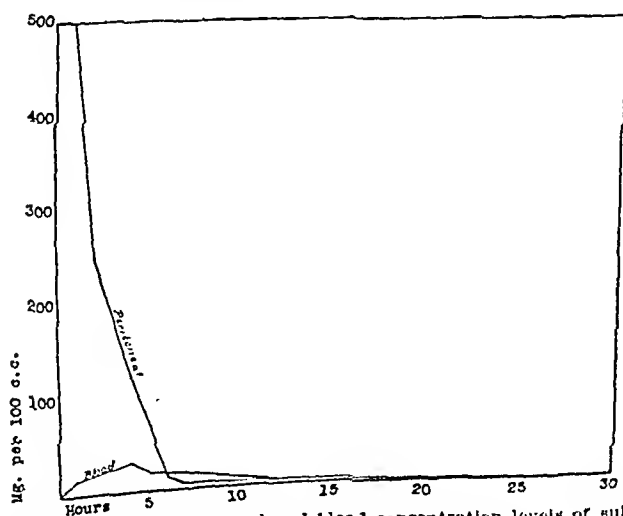


Fig. 2.—Comparison of intraperitoneal and blood concentration levels of sulfanilamide hourly in rabbits after intraperitoneal implantation of 1 gram.

others that little is to be gained. Fortunately, we see our cases early, but, in any event, operation is decided by the patient's immediate condition rather than by the relative area of peritonitis involved, or the time elapsed since its onset.

The bacteriology of appendiceal peritonitis has been shown to be far from specific; the various streptococci are found, anaerobes of the Welch type occur, but the colon group is to be considered the most common invader, and generally, our greatest foe. In ruptured peptic ulcers also streptococci and colon bacilli are chiefly the organisms found.<sup>5</sup>

In treating peritonitis with sulfanilamide given orally, Ravdin and co-workers<sup>1</sup> at first discontinued the drug in forty-eight to seventy-two hours in the earlier cases of their series when the culture failed to show hemolytic streptococci. Following the work of Helmholz,<sup>6</sup> who demonstrated the effectiveness of sulfanilamide against *Escherichia coli*, they then employed it in all cases when this organism was found, then, "before long it was employed in all cases regardless of culture report." Mellon and collaborators,<sup>7</sup> too, in commenting on the wholly unanticipated therapeutic properties of sulfanilamide given by the usual routes and the extensive nonspecificity of its action is reminded by its remarkable behavior of a "general internal disinfectant."

Perhaps some criticism may be forthcoming of one phase of the surgical technique employed, namely, the "lavage" of the infected peritoneal cavity. In the usual early case of ruptured appendix certainly no attempt is made to lavage the entire abdomen. When tenable, the field contaminated by free pus is walled off by gauze packs and the area washed clean by alternate perfusion with warm normal saline solution and suction. Gangrenous and devitalized tissue is removed when possible, the appendix is never left behind. Walled-off collections of pus and appendiceal abscesses are likewise washed out, with the usual respect as to formed natural barriers. On the other hand, when the whole peritoneal cavity has been contaminated by the sudden rupture of an ulcer, and infective material and gross food particles are strewn among the bowel loops, all accessible areas are washed out in turn.<sup>8</sup> The senior author for many years has followed this procedure in ruptured ulcers, and regional lavage in appendiceal peritonitis with uniformly satisfactory results.

In 1938 Lockwood<sup>9</sup> showed that peptones ("pns," as encountered) markedly interfered with the bactericidal action of sulfanilamide on the hemolytic streptococci. Meleney and Harvey<sup>10</sup> noted that sulfanilamide given orally acted the most dramatically in early hemolytic streptococci infections in which tissue necrosis and thrombosed blood vessels were not present to prevent contact of the circulating drug with the invading organism. In the presence of tissue necrosis or abscess formation in infections, efficacy of sulfanilamide has been found definitely limited, and debridement and surgical drainage must be done to effect healing.



TABLE I

SHOWING HOURLY BLOOD SULFANILAMIDE CONCENTRATION IN RABBITS RECEIVING ONE GRAM OF SULFANILAMIDE INTRAPERITONEALLY

TIME (HOUR) BLOOD SULFANILAMIDE CONCENTRATION MG./100 C.C.					
	RABBIT I	RABBIT II	RABBIT III	RABBIT IV	AVERAGE
1	6.8	7.0	4.0	13.0	7.7
2	7.3	10.0	6.0	15.0	9.5
3	12.9	26.0	16.0	17.0	18.0
4	18.0	28.0	17.0	24.8	22.0
5	17.2	26.0	15.0	23.0	20.3
6	17.2	25.0	10.0	22.5	18.7
7	17.0	22.0	8.0	22.0	17.2
8	16.8	18.5	6.0	21.8	15.7
9	14.5	17.8	5.8	20.5	15.4
10	12.0	17.0	5.4	19.2	13.4
13	4.5	15.0	4.2	16.0	10.0
18	3.8	9.6	4.0	10.5	6.9
24	2.8	3.2	3.8	4.5	3.7
30	2.6	0.5	2.0	0.3	1.3

10.8 mg.; Case 7, thirteen grams showed 13.1 mg.; Case 9, ten grams showed 9.4 mg.; Case 12, ten grams showed 9.4 mg.; Case 13, six grams showed 10.2 mg., Case 14, eight grams showed 6.1 mg., and Case 24, nine grams showed 7.9 mg.

The maximum blood concentration of sulfanilamide was reached almost uniformly in three hours in patients as compared to four hours in rabbits. In older individuals, the gradient is not as steep, perhaps due to natural cardiovascular and renal changes.

No significant pathologic changes, gross or microscopic, were seen in the intestines or peritoneum of rabbits following direct contact of these tissues with sulfanilamide crystals by intraperitoneal implantation.

## DISCUSSION

No effort has been made to classify our peritonitis cases into the classically described local, spreading, and general forms, feeling with

TABLE II

COMPARING HOURLY INTRAPERITONEAL AND BLOOD CONCENTRATION OF SULFANILAMIDE IN RABBITS

TIME (HOUR)	BLOOD CONCENTRATION INTRAPERITONEAL CONCENTRATION	
	MG./100 C.C.	MG./100 C.C.
1	15.0	500
2	20.0	215
3	26.0	180
4	30.0	120
5	20.0	70
6	19.5	20
7	18.5	8
8	15.0	5
9	11.0	4
10	10.0	4
12	4.0	4
15	4.0	3
20	3.0	2
25	2.0	1
30	0.5	trace

No.	Sex	Diagnosis	Days	Operation	Specimen	No.	Course
11	M	Acute right salpingo oophoritis (gonococci) with peritonitis	5 hr.	Salpingo oophorectomy right	8 Gm.	No	Uneventful p.o. course. Afebrile 9th p.o. day and discharged ambulatory on the same day.
12	M	Perforated gastric carcinoma	5 days	Subtotal gastrectomy	8 Gm.	No	Excision on 8th p.o. day. Excacerbation of pulmonary tuberculosis.
13	M	Ruptured retrocecal appendicitis (100 c.c pus in pelvis)	5 hr.	Appendectomy	10 Gm.	No	Wound hematoma. Discharged on 7th p.o. day.
14	M	Ruptured pelvic appendicitis	5 hr.	Appendectomy	6 Gm.	No	Wound hematoma. Discharged ambulatory on 8th p.o. day.
15	M	Ruptured appendicitis	24 hr.	Appendectomy	8 Gm.	No	Wound infection. Discharged on 7th p.o. day.
16	F	Ruptured retrocecal appendicitis (100 c.c pus aspirated)	1 day	Appendectomy	8 Gm.	No	Fecal fistula. Discharged from hospital on 22nd p.o. day with fecal fistula still draining.
17	M	Appendiceal abscess	7 days	Appendectomy	1 Gm.	Yes	Uneventful p.o. course. Afebrile on 4th p.o. day. Discharged 8th p.o. day.
18	M	Ruptured retrocecal appendicitis	6 days	Appendectomy	1 Gm.	No	Wound infection. Discharged on 13th p.o. day.
19	M	Appendiceal abscess	3 days	Appendectomy	8 Gm.	Yes	Uneventful p.o. course. Afebrile on 4th p.o. day. Discharged on 5th p.o. day.
20	F	Perforated laterocecal appendicitis (gangrenous)	24 hr.	Appendectomy	8 Gm.	Yes	Wound infection. Discharged on 9th p.o. day.
21	F	Ruptured subcecal appendicitis	16 hr.	Appendectomy	3.5 Gm.	No	Wound hematoma. Discharged on 7th p.o. day.

TABLE III

CASE NO.	AGE	SEX	DIAGNOSIS	DURATION OF SYMPTOMS	PROCEDURE	SULFANILAMIDE	DRAIN	POSTOPERATIVE COURSE
1	15	M	Ruptured pelvic appendicitis	3 days	Appendectomy	1 Gm.	Yes	Afebrile on 2nd p.o. day. Discharged on 9th p.o. day. No complication.
2	54	M	Stab wound in small intestine	10½ hr.	Simple closure	8 Gm.	Yes	Afebrile on 2nd p.o. day. Uneventful p.o. course. Discharged 13th p.o. day.
3	40	M	Perforated gastric ulcer	18 hr.	Simple closure with gastroenterostomy	10 Gm.	No	Afebrile on 4th p.o. day. Uneventful p.o. course. Discharged 9th p.o. day.
4	20	M	Ruptured pelvic appendicitis	8½ hr.	Appendectomy	8 Gm.	No	Uneventful p.o. course. Discharged on 7th p.o. day.
5	56	M	Perforated appendicitis (50 c.c. pus in pelvis)	2 days	Appendectomy	9 Gm.	No	Uneventful p.o. course. Discharged on 7th p.o. day.
6	36	F	Perforated duodenal ulcer	6 hr.	Simple closure	10 Gm.	No	Uneventful p.o. course. Afebrile 4th p.o. day. Discharged 13th p.o. day.
7	26	M	Ruptured retrocecal appendicitis	24 hr.	Appendectomy	13 Gm.	No	Uneventful p.o. course. Afebrile 2nd p.o. day. Discharged 7th p.o. day.
8	48	M	Ruptured retrocecal appendicitis	39 hr.	Appendectomy	8 Gm.	No	Uneventful p.o. course. Discharged 7th p.o. day.
9	42	M	Perforated gastric ulcer	5 hr.	Simple closure	10 Gm.	No	Uneventful p.o. course. Discharged 9th p.o. day, ambulatory. Afebrile on 4th p.o. day.

Since starting to employ sulfanilamide intraperitoneally, we feel more than ever that lavage of the infected area is indicated to mechanically remove as much as possible the pus which serves as a deterrent to the action of sulfanilamide. All surgeons have been astounded at the amount of foul pus that can be aspirated from the pelvic cavity in cases of ruptured pelvic appendicitis (50 to 320 c.c. in our cases by actual measurement). We have seen the necrotic and "cooked" appearance of appendiceal "beds" when a gangrenous retrocecal appendix has ruptured and almost disintegrated in a pool of pus. We have closed with dams and drains and later spent many days changing the foul-smelling dressings, the veritable "pus compresses" which were sure to follow—anxious, miserable, expensive days for the patient, with always the threat of intestinal obstruction under an unsightly scar. This side of the picture is rarely presented, or glossed over, when surgical reports are written; it is taken for granted. Since sulfanilamide has been added to our armamentarium we have been able to close most of these cases confidently without drains, secure primary wound healing, and discharge these patients promptly after smooth postoperative courses.

Regardless of the amount of pus in the abdomen, we limit drainage to only those cases with extensive irremovable devitalization of tissue. Lockwood and Ravdin<sup>11</sup> in tabulating the improvement in appendicitis mortality since using sulfanilamide (parenterally and orally) show only one death in 318 cases, truly an admirable record. Still, 41 per cent of these cases were drained. It is our belief that the number of cases requiring drainage could be rendered exceedingly small by the local use of sulfanilamide, after adequate removal of pus by suction and judicious lavage of the infected area with normal saline solution. We feel that the so-called danger of "spreading the infection" has been highly overestimated, that in most cases the infection is at least microscopically well beyond the area actually touched by the saline lavage.

The experiments with rabbits revealed that even lethal doses of sulfanilamide crystals placed directly in the abdominal cavity showed neither gross nor microscopic evidence of tissue damage. The study of the blood concentration of sulfanilamide in our patients after intraperitoneal administration of the drug showed that absorption was quite rapid, reaching the maximum in three hours, and that for each gram of intraperitoneal sulfanilamide we could expect 1 mg. per cent concentration in the blood. In an experiment on dogs Ravdin and co-workers<sup>12</sup> demonstrated that one and one-half hours after administration of sulfanilamide by hypodermoclysis the peritoneal concentration was still less than one-half the blood level (41.6 to 43 per cent of blood level). Time being a precious element, especially in spreading peritonitis, we believe that the local use presents distinct advantages. Since the usual systemic medication aims to attain a blood level of 7 to 15

TABLE III—CONT'D

CASE NO.	AGE	SEX	DIAGNOSIS	DURATION OF SYMPTOMS	PROCEDURE	SULFANILAMIDE	DRAIN	POSTOPERATIVE COURSE
21	5	M	Appendical abscess	3 days	Appendectomy	4 Gm.	Yes	Wound infection. Discharged on 9th p.o. day.
22	15	M	Ruptured retrocecal appendicitis	37 hr.	Appendectomy	9 Gm.	No	Uneventful p.o. course.
23	13	F	Ruptured pelvic appendicitis	2 1/4 days	Appendectomy	7 Gm.	No	Wound infection. Discharged on 9th p.o. day.
24	25	M	Appendical abscess	12 days	Drainage only	8 Gm.	Yes	Afebrile on 6th p.o. day. Discharged on 9th p.o. day.
25	13	F	Ruptured retrocecal appendicitis	6 days	Appendectomy	4 Gm.	Yes	Afebrile on 3rd p.o. day. Discharged on 7th p.o. day.
26	7	M	Ruptured pelvic appendicitis	11 hr.	Appendectomy	4 Gm.	No	Partial bowel obstruction on 7th p.o. day.
27	12	F	Pneumococic peritonitis (50 c.c. pus aspirated)	1 day	Appendectomy	6 Gm.	No	Afebrile on 2nd p.o. day. Discharged on 8th p.o. day.
28	33	M	Ruptured appendicitis (60 c.c. pus aspirated)	12 hr.	Appendectomy	8 Gm.	No	Afebrile on 4th p.o. day. Discharged on 8th p.o. day.
29	27	M	Ruptured subcecal appendicitis	33 hr.	Appendectomy	4 Gm.	No	Afebrile 3rd p.o. day. Discharged 7th p.o. day.
30	62	M	Gangrenous cholecystitis and general peritonitis (65 c.c. exudate aspirated)	4 days	Cholecystostomy without peritoneal drainage	8 Gm.	Yes	No wound infection. Afebrile 2nd p.o. day. Discharged 14th p.o. day.

tion, enterocolostomy, gall-bladder operations, etc. We feel a sense of security after closure likened to that after Moynihan's "hypnotic stitch."

At the time this work was in early progress there was no medical literature extant describing the clinical use of sulfanilamide crystals in the peritoneal cavity. We found ourselves in the paradoxical position of trying to justify our successful cases. The literature on the sulfonamides is growing voluminous and it is gratifying to see that clinical as well as experimental reports appear to justify and indicate its intraperitoneal use.

Dees<sup>12</sup> reported a consecutive series of 25 cases of perforated appendices operated upon between November, 1939, and September, 1940. Only one patient was lost, operation being performed after an elapsed time of seven days, with the patient in a state of generalized peritonitis with abdominal distention. This author has used what seems to us an inordinately large amount of the drug, "A standard dose of sulfanilamide was used on all these cases: 20 grams," especially when his age group varied from four to sixty-eight years. No untoward drug reactions were recorded, and the author makes the interesting observation that "the greater the degree of peritonitis, the higher the blood concentration."

Key and Frankel<sup>13</sup> have further shown that in experimental animals sulfanilamide, sulfapyridine, and sulfamethylthiazole in powder form are well tolerated by the joints, muscles, and connective tissues. The drugs in solution were found well tolerated by joint, pleural, and peritoneal surfaces.

Recently Lockwood<sup>14</sup> has advanced a reasonable working hypothesis of the mode of action of sulfonamide drugs. These compounds bear a structural similarity to p-aminobenzoic acid, which is essential to bacterial nutrition. By virtue of this structural similarity the molecules of sulfanilamide are capable of competitively replacing molecules of p-aminobenzoic acid in the cycle of bacterial nutrition. The bacterial cells cease to divide and the resultant inhibition of bacterial reproduction may be called "bacteriostasis." Lockwood points out that "The concentration of sulfonamide required for complete bacteriostasis may be greater than is supplied the area through the physiologic process of drug transport. However, if the molecules of sulfonamide greatly outnumber the molecules of p-aminobenzoic acid, the bacteria cease to multiply, their toxin production stops, and they will die either from 'starvation' or by falling prey to the phagocytic cells of the host. When this sequence takes place in the body, the infection no longer spreads into new areas, the bacteria are destroyed, and the patient recovers."

P-aminobenzoic acid and the like substances present in pus and necrotic tissues, thus, in function, are sulfonamide inhibitors. It follows naturally that adequate removal of pus is of prime importance in treating purulent infections with sulfonamides, and peritonitis, we contend, should not be an exception.

mg. per cent, we have at hand a precise method of attaining the desired therapeutic blood level in peritonitis within three hours. Thus, recently we have routinely employed 8 to 10 Gm. on the basis of the above findings. As pointed out by Jensen and co-workers,<sup>4</sup> reasoning from the solubility of sulfanilamide at body temperature (0.8 per cent), we have achieved within a few minutes at the very site of infection a concentration nearing 800 mg. per cent. A concentration adequately bactericidal for some organisms and bacteriostatic for others is maintained safely beyond the time at which the usually desired therapeutic blood level has been reached.

As shown by Fig. 3, our patients have a sulfanilamide concentration in the blood of from 5 to 8 mg. per cent at the end of 12 hours following operation, and at the end of twenty-four hours, it is still between 3 and 5 mg. per cent. Because of the massive single dosage with its rapid absorption we were concerned whether any consistent deleterious effect might be produced on the normal leucocyte reaction. In several cases closely followed we found no depression of the leucocyte count, the degree of leucocytosis being generally compatible with the severity of the infection and the response of the host. Thus in patient S.K., the preoperative leucocyte count was 13,600 with 86 per cent polymorphonuclears, the second postoperative day 11,900 with 85 per cent polymorphonuclears. In patient K.S., the preoperative count was 19,100 with 92 per cent polymorphonuclears; first postoperative day 15,600 and 78 per cent polymorphonuclears; second postoperative day 9,300 with 77 per cent polymorphonuclears; fourth postoperative day 6,800 and 81 per cent polymorphonuclears. On patient Y. N., a perforated gastric carcinoma case, daily blood counts were done for eleven consecutive days. The preoperative count was 6,000 with 86 per cent polymorphonuclears; it was 7,400 with 91 per cent polymorphonuclears on the third postoperative day, and on the eleventh day, the count was 8,200. In patient M.F., the preoperative leucocyte count was 24,400 with 88 per cent polymorphonuclears; on the third postoperative day, the count was 21,400 with 90 per cent polymorphonuclears.

In our limited series of cases we have encountered no untoward toxic manifestations. The patients are remarkably serene and comfortable on the first postoperative day and are generally able to continue sulfanilamide medication and take fluids orally. The drug is given parenterally after surgery involving the stomach or bowels, or if nausea precludes oral administration. We have also discovered that in our female patients we have not recently encountered the hitherto occasional postoperative pyelitis and bladder infection. In passing, it may not be amiss to mention that in our service we feel we have almost overcome the surgeon's bugbear of wound abscesses by use of sulfanilamide prophylactically in operative wounds with potentiality of infection. It is likewise used intra-abdominally after gastric resec-

They recorded nine fatalities in thirty-one cases having positive cultures. Eight of the fatalities were associated with streptococcus. Among other things, their present technique includes suction removal of intraperitoneal and intrapelvic fluid, 5 to 10 Gm. sulfanilamide crystals sprinkled about the lesion with 3 to 5 Gm. in the abdominal wall, and the wound closure with silk using no intraperitoneal drains.

TABLE IV  
SUMMARY OF RESULTS

NATURE	NO. OF CASES	REMARKS
Ruptured appendicitis with peritonitis	18	
A. Primary closure of the wound without drain	15	
1. Primary healing of the wound	7	
2. Wound hematoma	3	
3. Wound infection	4	
4. Intraperitoneal infection—fecal fistula	1	
B. Closure of the wound with drain	3	
Appendical abscess with drain	4	
Perforated peptic ulcer (primary closure of wound without drain)	3	Wound healed per primam
Perforated gastric carcinoma (subtotal gastrectomy) with primary closure of wound without drain	1	Evisceration on eighth p. o. day. Wound healed per primam
Stab wound in the small intestine (closure of wound with drain)	1	
Acute salpingitis with pelvic peritonitis (without drain)	1	Wound healed per primam
Pneumococcal peritonitis	1	Wound healed per primam
Gangrenous cholecystitis with generalized peritonitis	1	Wound healed per primam

Jackson<sup>19</sup> of Ann Arbor recently reported on the intraperitoneal use of sulfanilamide. He recognized it as a sound procedure. In his studies of blood sulfanilamide concentration after intraperitoneal implantation of therapeutic amounts in patients and dogs he found the peak level at about two hours, falling rapidly to almost nothing at the end of twenty-four hours. Twenty-five patients received sulfanilamide intraperitoneally at the University of Michigan Hospital during the year, 1940-41, indications being peritonitis, large bowel surgery, and peritoneal soiling with contents of the gastrointestinal tract. No fatalities were recorded in the peritonitis cases except in those in which sulfanilamide was not continued. The only complication which caused concern was icterus in six patients which was felt due to liver damage. The jaundice cleared on discontinuing the drug. Checking in experimental animals it was found that during the absorptive phase sulfanilamide levels after intraperitoneal implantation were 30 to 40 per cent higher in the portal blood than in the jugular vein.



Impressed by the groundwork of Lockwood, Rosenberg and Wall<sup>15</sup> proceeded to experiment with peritonitis in rats. The peritonitis was produced by injecting pus from clinical cases of appendicitis and peritonitis. In a series of 42 white rats, 20 of a possible 21 unprotected rats died of peritonitis. However, 11 out of 21 rats protected by the simultaneous injection of a sulfanilamide suspension lived indefinitely. In another experiment, 48 rats were given sulfanilamide either intraperitoneally or subcutaneously, four to twenty hours after production of peritonitis. With intraperitoneal treatment 17 good results out of 24 were reported, as compared with the 7 good results out of a possible 24 when sulfanilamide was given subcutaneously. From the experiments, although admittedly not conclusive, the authors felt some degree of protection was afforded by intraperitoneal implantation, more so than by the subcutaneous route. They recommend intraperitoneal implantation of sulfanilamide in peritonitis cases augmented immediately by subcutaneous sulfanilamide. Four clinical cases of peritonitis were presented with recovery in all: two cases of appendiceal peritonitis, a case of gross peritoneal contamination from bowel punctures during operation for intestinal obstruction, and a case of appendiceal abscess with bowel obstruction and contamination.

Thompson, Brabson, and Walker<sup>16</sup> reported on the intraabdominal use of sulfanilamide in acute appendicitis at the Roosevelt Hospital during the year 1940. It was employed in a total of fifty-nine, or 29 per cent of 204 cases, chiefly in those with peritonitis or abscess formation. Not a single patient was lost during the year—a mortality rate of zero! This was compared with a series of 741 similar cases at the same hospital operated upon during the period 1935 to 1939, including simple acute, peritonitis and abscess cases. There were twenty deaths, or a mortality rate of 2.7 per cent. With employment of sulfanilamide complications seemed less frequent and less severe, no local tissue destruction was found, and no severe toxic effects were encountered. The authors point out that a mortality rate approximating zero must not be expected with sulfanilamide since dissociated conditions, such as embolism, cannot be obviated. They are firmly convinced, however, that the dramatic reduction in their mortality rate is directly attributable to sulfanilamide.

Graham<sup>17</sup> of Brooklyn now employs intraperitoneal and subcutaneous sulfanilamide in appendicitis with peritonitis, gastric and intestinal resections, closure of colostomies, operations for intestinal obstruction, and perforations of hollow abdominal viscera, "with greatly improved results." This author employs 4 Gm. of sulfanilamide in 500 c.c. saline solution as the initial intraperitoneal dose.

Griswold and Antonic<sup>18</sup> have analyzed 111 consecutive cases of perforated peptic ulcer seen from 1931 to 1940 at the Louisville City Hospital. They stress the importance of the streptococcus in relation to mortality and advocate the local implantation of sulfanilamide.

8. Tashiro, K., and Kobayashi, N.: Duodenal Ulcer in Infancy and Childhood, A Case of Perforated Duodenal Ulcer in a Child of Seven, *Am. J. Surg.* 29: 379-383, 1935.
9. Lockwood, John S.: Observations on the Mode of Action of Sulfanilamide and Its Application to Surgical Infections, *Ann. Surg.* 108: 801-807, 1938.
10. Meleney, F. L., and Harvey, H. D.: The Combined Use of Zinc Peroxide and Sulfanilamide in the Treatment of Chronic, Undermining, Burrowing Ulcers Due to the Micro-Aerophilic Hemolytic Streptococcus, *Ann. Surg.* 110: 1067-1094, 1939.
11. Lockwood, J. S., and Ravdin, I. S.: The Prophylactic Use of Sulfanilamide in Abdominal Surgery, *SURGERY* 8: 43-55, 1940.
12. Dees, J. G.: A Valuable Adjunct in Perforated Appendices, *Mississippi Doctor* 18: 215-217, 1940.
13. Key, J. A., and Frankel, C. J.: The Local Use of Sulfanilamide, Sulfapyridine and Sulfamethylthiazol, *Ann. Surg.* 113: 284-297, 1941.
14. Lockwood, J. S.: Sulfonamide Therapy as an Aid to Surgery, *Surg., Gynec. & Obst.* 72: 307-311, 1941.
15. Rosenberg, S., and Wall, N. M.: The Treatment of Diffuse Peritonitis by the Direct Intraperitoneal Introduction of Sulfanilamide, *Surg., Gynec., & Obst.* 72: 568-578, 1941.
16. Thompson, J. E., Brabson, J. A., and Walker, J. M.: The Intraabdominal Application of Sulfanilamide in Acute Appendicitis, *Surg., Gynec. & Obst.* 72: 722-727, 1941.
17. Graham, H. F.: The Subcutaneous and Intraperitoneal Use of Sulfanilamide, *S. Clin. North America* 21: 577-579, 1941.
18. Griswold, R. A., and Antonicic, R. F.: Perforated Peptic Ulcer, *Ann. Surg.* 113: 791-801, 1941.
19. Jackson, H. C.: Intraperitoneal Sulfanilamide, *Ann. Surg.* 113: 1069-1070, 1941. (Abstract of paper delivered before the First Annual Assembly of The Central Surgical Association).

## SUMMARY AND CONCLUSION

1. A consecutive series of peritonitis cases have been presented in which sulfanilamide crystals were implanted intraperitoneally and the abdomen generally closed without drainage. There were no untoward reactions, no intra-abdominal complications, wounds healed per primam, and the patients were discharged promptly after generally smooth post-operative courses.

2. Collateral studies done on rabbits revealed that intraperitoneal absorption of sulfanilamide was very rapid, maximum absorption being in four hours; however, an extremely high concentration was maintained intraperitoneally until the maximum blood concentration was reached. No pathologic changes, gross or microscopic, were discovered in the peritoneal tissues even after contact with lethal doses of sulfanilamide crystals.

3. Blood sulfanilamide levels determined on patients receiving sulfanilamide intraperitoneally revealed that the maximum blood concentration was attained in three hours, and that for each gram placed intra-abdominally we could expect 1 mg. per 100 c.c. concentration in the blood.

4. In cases of peritonitis we have at hand a precise method for rapidly attaining a desired therapeutic level of sulfanilamide in the blood while establishing immediately at the site of infection a concentration of sulfanilamide impossible to attain by other methods, a concentration adequately bactericidal for some organisms and bacteriostatic for others.

5. The series of cases presented is admittedly small, but we feel with confidence that time will only add to the total increment of cases successfully treated, with no more peril than that associated with sulfanilamide in other fields of therapy. From our observations, we believe that the intraperitoneal use of sulfanilamide is a safe, rational, and effective procedure.

## REFERENCES

1. Ravdin, I. S., Rhoads, J. E., and Lockwood, J. S.: The Use of Sulfanilamide in the Treatment of Peritonitis Associated With Appendicitis, *Ann. Surg.* 3: 53-63, 1940.
2. Foerster: *Zentralbl. f. Haut- u. Geschlechtskr.* 45: 549, 1933 (quoted from Long and Bliss).
3. Long, P. H., and Bliss, E. A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, 1939, The Macmillan Co.
4. Jensen, N. K., Johnsrud, L. W., and Nelson, M. C.: The Local Implantation of Sulfanilamide in Compound Fractures, *Surgery* 6: 1-12, 1939.
5. Davison, M., Aries, L. J., and Pilot, T.: A Bacteriological Study of the Peritoneal Fluid in Perforated Peptic Ulcers, *Surg., Gynec. & Obst.* 68: 1017-1020, 1939.
6. Helmholz, H. F.: The Use of Sulfanilamide as an Urinary Antiseptic, *J. Pediat.* 11: 243-247, 1937.
7. Mellon, R. R., Gross, P., and Cooper, T. B.: Sulfanilamide Therapy of Bacterial Infections, Springfield, Ill., 1935, Charles C Thomas, p. 312.

8. Tashiro, K., and Kobayashi, N.: Duodenal Ulcer in Infancy and Childhood, A Case of Perforated Duodenal Ulcer in a Child of Seven, *Am. J. Surg.* 29: 379-383, 1935.
9. Lockwood, John S.: Observations on the Mode of Action of Sulfanilamide and Its Application to Surgical Infections, *Ann. Surg.* 108: 801-807, 1938.
10. Meleney, F. L., and Harvey, H. D.: The Combined Use of Zinc Peroxide and Sulfanilamide in the Treatment of Chronic, Undermining, Burrowing Ulcers Due to the Micro Aerophilic Hemolytic Streptococcus, *Ann. Surg.* 110: 1067-1094, 1939.
11. Lockwood, J. S., and Ravid, I. S.: The Prophylactic Use of Sulfanilamide in Abdominal Surgery, *Surgery* 8: 43-55, 1940.
12. Dees, J. G.: A Valuable Adjunct in Perforated Appendices, *Mississippi Doctor* 18: 215-217, 1940.
13. Key, J. A., and Frankel, C. J.: The Local Use of Sulfanilamide, Sulfapyridine and Sulfamethylthiazol, *Ann. Surg.* 113: 284-297, 1941.
14. Lockwood, J. S.: Sulfonamide Therapy as an Aid to Surgery, *Surg., Gynec. & Obst.* 72: 307-311, 1941.
15. Rosenburg, S., and Wall, N. M.: The Treatment of Diffuse Peritonitis by the Direct Intraperitoneal Introduction of Sulfanilamide, *Surg., Gynec., & Obst.* 72: 568-578, 1941.
16. Thompson, J. E., Blabson, J. A., and Walker, J. M.: The Intraabdominal Application of Sulfanilamide in Acute Appendicitis, *Surg., Gynec. & Obst.* 72: 722-727, 1941.
17. Graham, H. F.: The Subcutaneous and Intraperitoneal Use of Sulfanilamide, *S. Clin. North America* 21: 577-579, 1941.
18. Griswold, R. A., and Antonic, R. F.: Perforated Peptic Ulcer, *Ann. Surg.* 113: 791-801, 1941.
19. Jackson, H. C.: Intraperitoneal Sulfanilamide, *Ann. Surg.* 113: 1069-1070, 1941. (Abstract of paper delivered before the First Annual Assembly of The Central Surgical Association).

# THE EFFECT OF SULFANILAMIDE CRYSTALS, USED TOPICALLY, ON THE FATE OF TRANSPLANTED BONE

SOME EXPERIMENTAL AND CLINICAL OBSERVATIONS

THOMAS HORWITZ, M.D., PHILADELPHIA, PA.

**S**ULFANILAMIDE and its derivatives are being employed in bone and joint surgery as a prophylactic measure to prevent the relighting, by the trauma of surgical intervention, of a pre-existing, quiescent infection. Indeed, this measure has been suggested as a routine step in surgery of clean bone and joint cases without any history of preceding infection.

Although the use of local chemotherapy has been recommended in bone grafting procedures, the use of the sulfonamide compounds in this field of surgery will depend, among other things, upon proof that these drugs are not deleterious to the normal process of incorporation of a bone graft by the host bone. The purpose of this communication is to offer experimental evidence and some clinical proof that the local use of sulfanilamide in powder form has no adverse effect on the fate of transplanted bone.

## EXPERIMENTAL METHODS AND MATERIALS

Eighteen adult rabbits, weighing between 2,000 and 4,000 Grams, were operated upon under ether anesthesia. In 6 animals a graft was removed from one tibia and transplanted to a prepared bed on the opposite tibia, while a graft from the latter tibia was transferred to the former limb. One wound, serving as a control, was closed in layers without the use of any drug locally. The other wound was packed and the bone graft surrounded with sulfanilamide crystals in 4 rabbits and sulfathiazole crystals in 2 rabbits and the wound was closed in layers. In 2 animals the above procedure was pursued without using any drug in either leg. In 2 rabbits, a segment was resected from one ulna and was transplanted to an identical defect in the opposite ulna, and this step was reversed, the radius acting as a splint for the extremity. Sulfanilamide crystals were packed into the wound of one limb, after closure of the opposite control wound into which no drug had been introduced. In 8 rabbits, bone was transplanted from the iliac crest to prepared sites on both tibiae, one leg wound being packed with sulfanilamide crystals in 7 animals and with sulfathiazole crystals in 1 animal, after closure of the opposite control wound into which no drug had been implanted.

The powdered drugs were not sterilized. No postoperative fixation was employed other than firm adhesive dressings. The animals were killed at intervals of one, two, four, six, and eight weeks following operation, and the operated bones were removed, roentgenographed, and examined histologically.

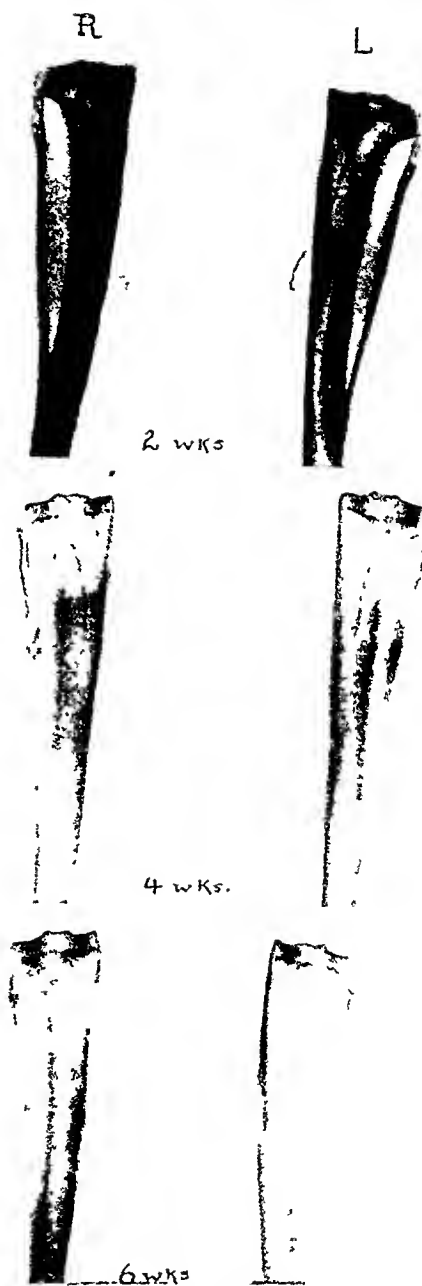
*Remarks.*—It was my opinion (and this has been held by Key and Burford<sup>1</sup> in their experimental work) that the concentration of the drug was not maintained long enough to affect the fate of the bone graft of the opposite control side wherein no drug had been implanted locally, and that the use of a control in the same animal was preferable to using different animals of approximately the same size, age, sex, and weight. To offset any criticism, however, the experiment was repeated in the tibiae of two rabbits, without using any drug. The features of the incorporation of bone graft by host bone were identical, roentgenographically and histologically, with those in the control legs of the other experimental animals, wherein no drug had been implanted locally.

No effort was made to sterilize the drug and there were no indications, grossly or microscopically, of postoperative infection. This evidence, supported by some clinical experience, suggests that the sulfamido drugs may be sufficiently bacteriostatic not to require sterilization for their local use. Some authors (Key, Frankel, and Burford;<sup>2</sup> Mueller<sup>3</sup>) recommend sterilization of the drug for local use, while others (Stueck, Maxwell, and Monsalvo;<sup>4</sup> Herrell and Brown<sup>5</sup>) consider this to be unnecessary.

*Observations.*—Roentgenographically, the transplanted bone graft was united to the host bone in both treated and control limbs by the fourth week, although a distinct zone of demarcation was still evident. The graft was well incorporated by the sixth week and by the eighth week it was indistinguishable from the host bone (Figs. 1 and 2).

Grossly, the bone transplant was firmly united to the host bone, in both drug-treated and control limbs, by the fourth week. Histologically, the fate of the bone transplant was identical in the treated and control bones. The main mass of the bone graft was seen to sequestrate and die, except for some viable cellular elements at its periphery. The graft was gradually removed by vascular resorption, slight osteoclastic activity, and the ingrowth of very cellular connective tissue in which new bone was formed. The adjacent periosteal tissues also demonstrated considerable osteoblastic activity. These processes of fibrous tissue invasion, metaplasia, and replacement of dead bone by young living bone occurred concomitantly. Except for isolated fragments of dead bone, the original graft had been almost entirely replaced by the eighth week.

In those wounds where the sulfonamide drugs were implanted locally, the fibroblastic reaction of the parosseous tissues appeared excessive.



Figs. 1 and 2—Roentgenograms of the left (sulfanilamide treated) and right (control) tibiae of rabbits that were killed at periods of two, four, six, and eight weeks following operation. In each instance the bone graft to the tibia had been removed from the left iliac crest. While there are slight differences in the roentgenographic appearance of the transplanted bone on the two sides in one of the specimens due to some variation in the size and integrity of the grafts the essential features of incorporation of the transplanted bone by the host bone appear to be identical in the drug-treated and control extremities.

This was possibly an expression of reaction to the crystalline foreign substance, although other evidences of foreign body reaction, such as inflammatory cells and giant cells, were not evident. Indeed, crystals of the implanted drugs were not evident in the specimens as early as two weeks postoperatively.

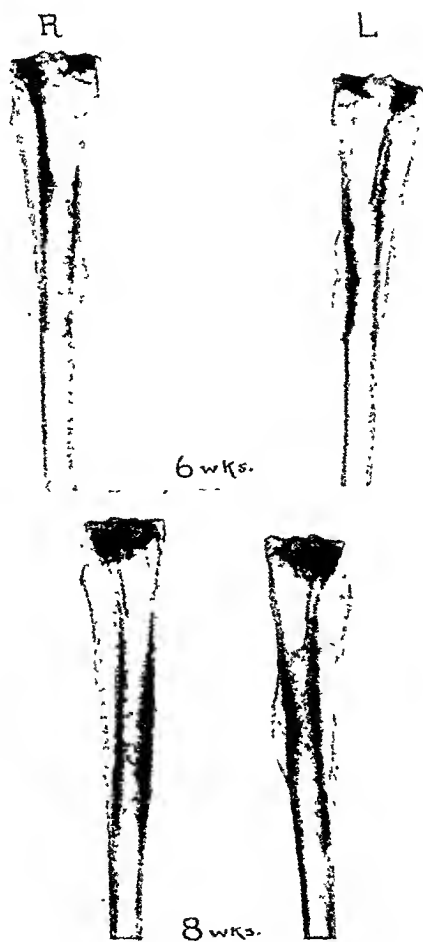


Fig. 2.—See opposite page for legend.

#### CLINICAL MATERIAL

I utilized sulfanilamide crystals in five patients in whom massive bone grafts were employed. In three of these cases distinct infection was present at the time of operation. One of the three infected patients, a 56-year-old white male, had an extra-articular fusion for a progressively destructive tuberculous arthritis of the wrist, despite the presence of multiple draining sinuses that were secondarily infected with a variety of streptococci and staphylococci. The second patient, a 14-year-old



white male, with a congenitally deformed foot and ankle, gave a history of infection following operation on the affected foot thirteen years previously. During a panarthrodesis procedure, a pocket of pus was exposed, from which a pure culture of *Staphylococcus aureus* was grown. In the third patient, a 51-year-old colored male, the field of a second-stage bone graft for a tuberculous spondylitis was contaminated from a pocket of pus at the upper end of the first graft, which had been inserted four weeks previously. Sulfanilamide was implanted locally in the fourth, potentially infected, case, at the site of a bone transplant for nonunion of the tibia following an infected compound fracture. The fifth case was a clean case without a history of preceding infection, in which a bone graft had been employed for a tuberculous spondylitis.

In all of the cases the operative procedure was completed with primary closure of the wound after local implantation of 4 to 16 Gm. of powdered sulfanilamide (sterilized drug in four patients, unsterilized drug in one). The sulfanilamide level of the blood in each case was maintained by the oral route for one week postoperatively. The infection was completely controlled in the three infected cases and in the one potentially infected case, all wounds healing by primary intention. In the 4 cases in which bone grafts were employed for arthrodesing purposes, the transplanted bone became well incorporated and the fusions were solid by the fourth postoperative month. It is too early to evaluate the ultimate fate of the bone graft in the case with tibial nonunion, but the progress of its incorporation thus far has been most satisfactory.\*

*Remarks.*—It cannot be denied that the fortunate outcome in the three actively infected cases and one potentially infected case might have occurred without the use of the drug. The experience in my five cases, however, corroborates the experimental evidence previously defined and indicates that the local use of the powdered sulfonamide compounds exerts no untoward or deleterious effect on the fate of a bone graft. An extensive, well-controlled trial will be necessary before any reliable conclusions are established as to the merits of local chemotherapy in bone graft surgery. The experience of Campbell and Smith<sup>6</sup> is of limited value in this respect. These authors, in their report in 1940, had reduced the incidence of infection following bone graft procedures in healed compound fractures with latent or potential infection, by the use of the sulfadruugs, from approximately 50 per cent (in a series of 261 onlay bone graft operations performed prior to the use of the drugs) to less than 25 per cent. They failed, however, to record how the sulfonamides had been administered in all of these cases, but it was evident that in some of them the oral route alone had been employed.

\*Solid union has occurred in this case. Sterilized sulfanilamide powder has been implanted, locally, at the time of bone-grafting procedure. In two other cases of tibial nonunion following infected compound fractures, without evidence of relighting of the old infection and with satisfactory progress in the incorporation of the transplanted bone by the host bone.

## DISCUSSION

The sulfonamide drugs are being employed topically in civil and war surgery, as a powder, solution, or ointment with or without the supplemental use of the drug systemically, in the prevention and active treatment of infections, due to susceptible bacteria, of the skin, mucous membrane, subcutaneous tissue, muscle, bone, viscera, joint spaces, and serous cavities. The local use of these drugs in contaminated or potentially infected fracture wounds has been largely a prophylactic measure (Jensen, Johnsrud and Nelson;<sup>7</sup> Key and Burford;<sup>1</sup> Stuck, Maxwell, and Monsalvo;<sup>4</sup> Campbell and Smith<sup>6</sup>). The topical use of these compounds has been extended to all types of bone and joint surgery where it is feared that a pre-existing infection may be relighted and to extensive procedures where there is considerable damage to the tissues or where metallic foreign bodies are left in the wound (Key and Burford;<sup>1</sup> Key, Frankel and Burford;<sup>2</sup> Campbell and Smith;<sup>6</sup> Key and Frankel;<sup>8</sup> Key<sup>9</sup>). This measure has been utilized as a routine step in clean bone and joint surgery (Key;<sup>9</sup> Key and Burford<sup>10</sup>). The sulfamido compounds are being used locally in the active treatment of acute and chronic bone and joint infections (Key;<sup>9</sup> Dickson, Diveley, and Kiene<sup>11</sup>).

*Mode of Action of the Sulfonamide Compounds.*—These drugs produce their effect on infections by exercising a bacteriostatic effect on certain susceptible organisms. Their curative action is maximal when (1) the concentration of the drug is high, (2) the local cellular defense is most active, and (3) the concentration of "sulfamide inhibitors" in the wound is minimal (Lockwood<sup>12</sup>). The sulfonamides are, therefore, of greatest value in the prevention of infection.

The topical application of these compounds insures a high local concentration in the tissues. Where the systemic administration of sulfanilamide may produce a concentration of 10 to 15 mg. per cent in the blood and tissue fluids, the local implantation of the crystalline powder of this drug, the most soluble of the sulfamides, makes possible a saturated solution and produces a concentration of 800 to 1,000 mg. per cent (Jensen, Johnsrud, and Nelson;<sup>7</sup> Key and Burford;<sup>1</sup> Stuck, Maxwell, and Monsalvo<sup>4</sup>). This concentration of this drug is not limited to the wound itself but extends into the surrounding tissues and remains constant until the drug is entirely absorbed. This concentration in the wound lasts approximately forty-eight hours; that is, until the drug is completely absorbed and excreted. It is probable that the concentration of sulfathiazole and the other less soluble sulfonamides lasts longer (Key;<sup>9</sup> Key and Burford<sup>10</sup>). The only dangers in the topical administration of the sulfonamides are the possibility of some interference with wound healing and of the uncontrollable toxic reactions in susceptible individuals.

*Reactions of Local Tissues.*—Although some observers (Thompson, Brabson, and Walker,<sup>13</sup> Mayo and Miller<sup>14</sup>) have felt that healing is stimulated by the sulfonamides, others (Veal and Klepser<sup>15</sup>) have noted

a deleterious effect of powdered sulfanilamide on normal cellular activity. That the local tissues are not inert to this powdered drug is indicated by the pathologic studies on rats by Davis, Harris, and Schneisser,<sup>16</sup> who observed a local nonspecific foreign body reaction to the crystalline compound. Key and his co-workers<sup>1, 2, 8</sup> observed no untoward effects in their experimental animals of the locally applied sulfonamides on the healing properties of wounds of muscle, subcutaneous tissue, fascia, bone, and joint cartilage. In their clinical experience, however, wounds so treated occasionally did not heal normally, and this was most apt to occur if too much drug had been implanted locally.

In my experimental animals, except for an exaggerated noninflammatory fibroplasia at the site of the transplanted bone, there was no undue foreign body reaction, and incorporation of the bone graft by the host bone progressed at a normal rate. In my limited clinical material, the wounds healed per primam and the progress of the bone graft in the various procedures appeared to be normal.

*Absorption of the Sulfonamide Drugs When Implanted Locally.*—The blood level is of no great significance in local prophylaxis. It will depend on a number of factors: the amount of drug used, the solubility of the drug, the size of the absorbing surface, the time interval following implantation, and the nature and vascularity of the absorbing surface. Key and Burford<sup>10</sup> made determinations of the blood concentration of sulfanilamide in several patients after local use of this drug in clean operative wounds, and they noted that this concentration varied from 1 to 9.2 mg. per cent (the latter reading having been made where 10 Gm. were implanted locally) on the first and second postoperative days, and that only a trace was present on the third day after operation. They observed a level of from 2 to 4 mg. per cent in the blood when 5 Gm. of the drug were used locally. In my clinical material the sulfanilamide levels dropped rapidly after the initial twenty-four to thirty-six hours and were sustained only by the supplemental oral administration of the drug. My observation is in keeping with the recent studies of Tocantins<sup>17</sup> and of Tocantins and O'Neill;<sup>18</sup> that is, absorption from a bone in which the medullary cavity had been exposed appeared to be more rapid, with an earlier blood level peak and subsequent fall, than when the marrow cavity was not exposed. This would suggest that where the medullary cavity of a bone has been exposed for the reception of or by the removal of a graft, and where the sulfonamides are implanted locally, the local effect should be prolonged by applying a portion of the drug to the overlying soft tissues as they are closed in layers. This would also serve to avoid the too rapid occurrence of a high systemic concentration of the drug.

#### CONCLUSIONS

The topical application of the sulfonamide compounds as prophylactic bacteriostatic agents in bone graft surgery of potentially infected or

even contaminated cases may serve to insure better anatomical and functional end results over a shorter period of time. The clinical trial of this measure will be dependent upon proof that the sulfonamide drugs, when employed topically, are not deleterious to the normal process of incorporation of transplanted bone by host bone. Experimental observations in eighteen rabbits and a limited clinical experience with five human cases indicate that the local implantation of sulfanilamide crystals has no apparent adverse effect on the fate of transplanted bone.

#### REFERENCES

1. Key, J. A., and Burford, T. H.: The Local Implantation of Sulfanilamide in Compound Fractures. Its Effect on Healing, *South. M. J.* 33: 449-455, 1940.
2. Key, J. A., Frankel, C. J., and Burford, T. H.: The Local Use of Sulfanilamide in Various Tissues, *J. Bone & Joint Surg.* 22: 952-958, 1940.
3. Mueller, R. S.: Use of Powdered Crystalline Sulfanilamide in Surgery, *J. A. M. A.* 116: 329, 1941.
4. Stuck, W. G., Maxwell, E. A., and Monsalvo, R. N. O.: Crystalline Sulfanilamide in Compound Fractures, *Texas State J. Med.* 36: 225-228, 1940.
5. Herrell, W. E., and Brown, A. E.: Local Use of Sulfamide Compounds in the Treatment of Infected Wounds, *Proc. Staff. Meet., Mayo Clin.* 15: 611-615, 1940.
6. Campbell, W. C., and Smith, H.: Sulfanilamide and Internal Fixation in the Treatment of Compound Fractures, *J. Bone & Joint Surg.* 22: 959-972, 1940; Sulfamide and Internal Fixation in the Treatment of Compound Fractures, *South. Surgeon* 10: 409-426, 1941; Fresh Compound Fractures, Treatment by Sulfonamides and by Internal Fixation in Selected Cases, *J. A. M. A.* 117: 672-675, 1941.
7. Jensen, N. K., Johnsrud, L. W., and Nelson, M. C.: The Local Implantation of Sulfanilamide in Compound Fractures. A Preliminary Report, *SURGERY* 6: 112, 1939.
8. Key, J. A., and Frankel, C. J.: The Local Use of Sulfanilamide, Sulfapyridine and Sulfamethylthiazol, *Ann. Surg.* 113: 284-292, 1941.
9. Key, J. A.: The Use of Sulfanilamide and Sulfathiazole in Orthopedic Surgery; Chairman's Address, *J. A. M. A.* 117: 409-412, 1941.
10. Key, J. A., and Burford, T. H.: The Prophylactic Implantation of Sulfanilamide in Clean Operative Wounds for the Reduction of Postoperative Infections, *Surg., Gynec. & Obst.* 73: 324-332, 1941.
11. Dickson, F. D., Diveley, R. L., and Kiene, R.: The Use of Sulfathiazole in the Treatment of Subacute and Chronic Osteomyelitis, *J. Bone & Joint Surg.* 23: 516-520, 1941.
12. Lockwood, J. S.: Sulfonamide Therapy as an Aid to Surgery, *Surg., Gynec. & Obst.* 72: 307-311, 1941; Sulfanilamide and Its Derivatives in Surgical Infections. A Review. 1. The Mode of Chemotherapeutic Action of the Sulfonamides, *SURGERY* 10: 493-503, 1941.
13. Thompson, J. E., Brubson, J. A., and Walker, J. M.: The Intraabdominal Application of Sulfanilamide in Acute Appendicitis, *Surg., Gynec. & Obst.* 72: 722-727, 1941.
14. Mayo, C. W., and Miller, J. M.: Solution of Sulfanilamide in the Local Treatment of Wounds, *Proc. Staff. Meet., Mayo Clin.* 15: 609-611, 1940.
15. Veal, J. R., and Klepper, R. G.: Treatment of Pyogenically Infected Wounds by Topical Application of Powdered Sulfanilamide and Sulfanilamide Albion Ointment. Preliminary Report, *M. Ann. District of Columbia* 10: 61-64, 1941.
16. Davis, H. A., Harris, L. C., and Selmeisner, H. C.: The Toxic Effects of Sulfanilamide Upon Tissues of Rats, *J. Lab. & Clin. Med.* 25: 1263-1275, 1940.
17. Tocantins, L. M.: Rapid Absorption of Substances Injected into the Bone Marrow, *Proc. Soc. Exper. Biol. & Med.* 45: 292-296, 1940.
18. Tocantins, L. M., and O'Neill, J. F.: Infusion of Blood and Other Fluids into the Circulation via the Bone Marrow, *Proc. Soc. Exper. Biol. & Med.* 45: 782-783, 1940; Infusions of Blood and Other Fluids into the General Circulation via the Bone Marrow: Technique and Results, *Surg., Gynec. & Obst.* 73: 281-287, 1941.

## THE EMPLOYMENT OF COTTON SUTURE MATERIAL IN THE FIELD

ROBERT S. SPARKMAN, M.D.,\* AND WILLIAM H. WILLIAMS, M.D.,\*  
FORT GEORGE G. MEADE, MD.

*(From the First Evacuation Hospital, Fort Meade)*

DURING the maneuvers of the United States Army in North and South Carolina in the fall of 1941, the First Evacuation Hospital† was encamped on a sandy field near Rockingham, North Carolina. A tent hospital of approximately one-thousand bed capacity was erected, wherein medical and surgical care was provided for certain components of the First Army. A large tent was utilized for the housing of all facilities for the performance of major surgical procedures, which were undertaken over a period of forty-six days between October 26 and December 5.

The circumstances under which professional care was administered were presumably comparable in some respects to those which one might encounter in the field in wartime. Patients requiring emergency surgery arrived at the hospital in soiled field clothing after having passed rapidly through clearing stations and other forward echelons. The greater part of the preparation and sterilization of operating room supplies was performed by enlisted personnel, who also acted in the capacities of scrub nurses and circulating nurses. The problems of dust and insect control were considerable. The sides of the operating tent were screened; insecticidal solutions were sprayed throughout the tent at frequent intervals; cardboard compartments were erected within the tent to enclose the operating area. Although these measures were helpful, they did not afford a complete solution to the problem of insect and dust control, and, in spite of vigilance on the part of all operating room personnel, it was not a rare occurrence for a fly to alight upon the Mayo table during the course of an operation.

Inasmuch as circumstances here enumerated were felt to constitute a situation predisposing to wound contamination, considerable speculation arose as to the choice of the most satisfactory suture material.

The selection of cotton as a suture material for most cases was substantiated by the highly encouraging reports of those who had used it in contaminated cases, notably Meade and Ochsner,<sup>1, 2</sup> as well as by the previous experience of both of the writers. Indeed, it is the contention of Meade and Ochsner<sup>2</sup> that the most important use of nonabsorbable suture materials is in grossly contaminated wounds, and they state further that "this contention . . . is based upon the experience that

\*Captain, Medical Corps, Army of the United States.

†Reinforced by the Fifteenth and Forty-first Evacuation Hospitals and by the Sixty-first Surgical Hospital, and later by the Twenty-eighth Surgical Hospital.

Received for publication, Feb. 9, 1942.

the grossly contaminated abdominal wound closed with catgut is particularly likely to disrupt, probably because of two factors: (1) delay in wound healing because of the infection, and (2) early digestion of the suture material by the large amount of proteolytic ferment liberated from the leucocytes. In such an instance the coaptating suture becomes valueless before wound healing has been completed, or, in some instances, even started. If, however, a nonabsorbable suture, particularly cotton, is used, the wound is held intact until infection has subsided and complete healing has occurred." Moreover, in view of the limited nursing facilities which are to be expected in a field hospital, and because of the possible necessity of evacuation of patients over long distances to station hospitals early in convalescence, the added protection of nonabsorbable suture material seemed particularly desirable. Meade and Ochsner<sup>1</sup> have, in fact, made the pointed statement that cotton thread would be a very satisfactory suture in field hospitals in wartime.

During the period of encampment 124 appendectomies were performed. Cotton was employed as the only suture material in every case, with this exception: that fine plain catgut was used for ligation of the appendical stump in most instances in which the stump was inverted. The McBurney incision was used exclusively. There was no mortality in the group.

Cotton was of the ordinary nonmercerized variety, either in black or white. It was sterilized by boiling for 20 minutes or by autoclaving for 15 minutes at 15 pounds pressure, after having been wrapped on spools made of 4 cm. segments of soft rubber tubing. Size No. 80 cotton, usually black, was used for skin closure, while No. 100 white was used for ligation of blood vessels immediately beneath the skin. Either No. 50 or No. 80 cotton was employed in closure of the remaining layers of the McBurney wound, depending upon the individual preference of the operator. Exclusive of the peritoneum, which was always closed with a continuous suture, interrupted sutures were used throughout. Ligation of the mesoappendix was accomplished either with No. 50, No. 20, or No. 8 cotton, the larger sizes ordinarily having been employed when the operator desired to ligate the main bulk of the mesoappendix en masse. In twenty instances the appendical stump was not inverted, either because the operator preferred noninversion or because the extension of inflammatory reaction to the cecum contraindicated such a procedure. Inversion in the remaining 104 cases was accomplished with No. 50 or No. 80 cotton.

Prolonged scrubbing of the abdominal wall with soap and water was adopted as a routine preoperative measure. In cases exhibiting perforation or gangrene of the appendix, as well as in some additional cases where the degree of suppuration was extensive, sulfathiazole or sulfanilamide powder in 8 Gm. quantities was implanted in the peritoneal cavity, although on no occasion was either drug placed in the

wound itself. In every case the wound was subjected to copious irrigation with physiologic saline solution following the closure of each layer.

Of 124 specimens removed, 79, or 63.3 per cent, showed histopathologic evidence of acute suppuration, and 27 of the 79 showed gross evidence of gangrene at the time of removal. There were two instances of perforation (Case 97 and Case 113). In the first instance only local peritonitis was observed, whereas the second was associated with diffuse suppurative peritonitis. In two additional cases (Case 98 and Case 112) gross contamination occurred as the result of disruption in continuity of the wall of a gangrenous appendix during the course of its removal. In each of these four cases a narrow strip of soft rubber dam was placed down to the peritoneum, which was closed. Drains in each instance were removed on the fourth or fifth postoperative day, whereupon each of the wounds in question healed by first intention.

In the remaining 120 cases both the peritoneal cavity and the wound were closed without drainage. Conclusions regarding wound healing in this group are generally based upon a period of postoperative observation of eight days, inasmuch as uncomplicated cases were evacuated to Station Hospitals after elapse of that number of days. Subsequent written communications, however, have been received in 66 instances. In the group of 120 cases there were only four patients (Cases 3, 49, 56, and 78) in whom any variety or degree of wound complication was observed. In three of these (3, 56, and 78) a small collection of uninfected serous fluid was evacuated from the wound on one occasion only, for each case, whereafter it did not reappear. It is felt that these cannot be regarded as instances of wound infection. The one remaining patient (Case 49) developed a left femoral thrombophlebitis on his sixth postoperative day, and suffered disruption of his wound on the thirteenth postoperative day. Following the evacuation of a large quantity of purulent material, the wound healed by granulation. The incidence of wound infection, assuming this to be the only instance which can be so regarded, is 0.83 per cent in the series of 120 cases, and the incidence of wound complication of any sort, regardless of nature or degree, is 3.33 per cent.

In one patient (Case 70), regarding whom no specific mention has heretofore been made, there developed on the fifth postoperative day sudden evidence of generalized peritonitis, in consequence of which his abdomen was reopened at the site of his previous wound. It was apparent that an abscess had formed about the appendiceal stump (which had not been inverted) with subsequent rupture of the abscess into the general peritoneal cavity. The peritoneum, however, was sealed, and the appearance of the wound at the time of its re-entry was clearly that of primary healing. Convalescence and wound heal-

ing were uneventful following drainage of the abscess. No attempt was made to remove the cotton sutures which had been introduced at the first operation.

#### COMMENT

Because of our fear of increased incidence of postoperative pulmonary complications arising from the nature of our accommodations, the general policy was adopted of allowing patients to be out of bed on the second or third day following operation. No ill effects of any sort were observed therefrom. We should not have been able to permit such early locomotion with equal assurance had we not enjoyed the sense of added security arising from the use of nonabsorbable suture material. As a corollary to this it may be suggested that an analogous situation exists when it is necessary for soldiers who have been operated upon in the field of combat to be evacuated considerable distances by motor over rough terrain to hospitals in the rear echelons.

It is not to be presumed that the gratifyingly low rate of wound infection and wound complication achieved under circumstances tending to favor wound contamination is to be ascribed to the nonirritant features of cotton sutures alone. On the contrary, we were of the opinion that careful preoperative skin cleansing and copious irrigation of wounds were of primary importance in promoting uncomplicated wound healing.

Our experiences with cotton suture material are in entire support of the contentions of Meade and Ochsner, that cotton may be employed safely in clean, contaminated, or infected wounds. We encountered no evidence to indicate that cotton acts as a detriment to wound healing in any way. Similar conclusions have been reached by Thorek,<sup>4</sup> Guthrie,<sup>5</sup> Farris,<sup>6</sup> and Cannaday.<sup>7</sup>

Finally, of less importance but of sufficient significance to justify its mention, cotton possesses the additional advantages of being inexpensive, plentiful, easy to carry, and easy to sterilize. Meade and Long<sup>1</sup> state that the average cost of cotton in 100 surgical procedures was 11½ cents per case, whereas the cost of catgut, as computed from a series of 469 operations, was \$1.16 per case.

#### CONCLUSIONS

Cotton suture material has been employed in 124 consecutive appendectomies performed in a tent upon soldiers engaged in field maneuvers simulating warfare. The results obtained therein are regarded as a reasonable basis for the conclusion that cotton is a satisfactory suture material for field use in clean, contaminated, or infected wounds.

The authors wish to acknowledge their gratitude to the Army Medical Museum for the examination of pathologic specimens, and to the members of the Surgical Service of the First Evacuation Hospital Reinforced for their assistance in all phases of the clinical work.



## REFERENCES

1. Meade, W. H., and Ochsner, A.: Spool Cotton as a Suture Material, J. A. M. A. 113: 2230-2231, 1939.
2. Meade, W. H., and Ochsner, A.: The Relative Value of Catgut, Silk, Linen, and Cotton as Suture Materials, SURGERY 7: 485-514, 1940.
3. Meade, W. H., and Long, C. H.: Cotton as a Suture Material, J. A. M. A. 117: 2140-2143, 1941.
4. Thorek, P.: Experiences With Spool Cotton as a Suture Material, Am. J. Surg. 55: 118-120, 1942.
5. Guthrie, D.: in discussion on 3.
6. Farris, J. M.: in discussion on 3.
7. Cannaday, J. E.: in discussion on 3.

Address requests for reprints to 4700 Neola Drive, Dallas, Texas.

# THE USE OF ESTROGENIC SUBSTANCES IN THE PREOPERATIVE AND POSTOPERATIVE TREATMENT OF HYPERTHYROIDISM

AMBROSE H. STORCK, M.D., AND  
R. GORDON HOLCOMBE, JR., M.D., NEW ORLEANS, LA.

*(From the Department of Surgery, School of Medicine, Tulane University; Touro Infirmary; and the Charity Hospital of Louisiana)*

THE use of estrogenic substances in conjunction with the surgical treatment of hyperthyroidism has previously been discussed by one of us (A. H. S.).<sup>1</sup> As indicated in that brief report, employment of this form of therapy was based upon inhibiting the secretory activity of the anterior lobe of the hypophysis, thereby reducing the production of anterior pituitary thyrotropic hormone, a mechanism suggested by Sherwood and Bowers,<sup>2</sup> and later by Grumbrecht and Loeser.<sup>3</sup>

The low blood concentration of thyrotropin which has usually been found to exist in hyperthyroidism<sup>4-11</sup> implies that considerable improvement would not accompany a further reduction of thyrotropic hormone levels, and that any good effects following estrogen therapy are probably not the result of inhibition of thyrotropin production. However, not only has it been found<sup>12</sup> that in hyperthyroidism there is sometimes an increase in the amount of thyrotropin in the blood, but Starr and Patton<sup>13</sup> have shown that in hyperthyroidism there is an increased sensitivity to thyrotropin.

Because a lowering of basal metabolism was observed following the administration of estrogen to thyroidectomized animals, Sherwood<sup>14</sup> has concluded from his more recent studies that the basal metabolism lowering effect of estrogenic substances is due to a direct hormone antagonism in the tissues rather than to either a direct influence on the thyroid gland, or mediation through the pituitary gland and the anterior pituitary thyrotropic hormone. However, entirely apart from the beneficial effects which a lessening of thyrotropic hormone production might have by retarding stimulation of the thyroid gland, reduction of the direct metabolism-stimulating effects produced by certain pituitary extracts<sup>15-22</sup> is an additional mechanism whereby inhibition of pituitary secretion might contribute to the beneficial effects of estrogen therapy in hyperthyroidism. These latter findings, along with those<sup>23-25</sup> concerning the pituitary-thyroid relationship or the thyroid-stimulating effect of anterior pituitary thyrotropic hormone, coupled with the demonstrations<sup>14, 26-28</sup> of the basal metabolism-lowering effect of estrogenic substances in experimental hyperthyroid animals, constitute a rational basis for the administration of estrogen in conjunction with the surgical treatment of patients with hyperthyroidism.

Received for publication, Nov. 24, 1941.

Additional inferences which might be drawn from clinical observations concerning thyroid-pituitary-ovarian relationships at puberty, in pregnancy, in castrates, and at the menopause, as well as in obesity, Cushing's disease, Simmonds' disease, aeromegaly, myxedema, and hyperthyroidism are not included in this brief report.

Collateral estrogen therapy would seem to be especially appropriate when hyperthyroidism is severe, when there is unsatisfactory response to the usual methods of preoperative preparation, and during the intervals between multiple-stage operations. This report presents what are considered to be some significant favorable effects observed in five cases which received this supplementary therapy.

*Description of Cases Receiving Estrogen Therapy.*—The five patients to whom estrogen therapy was given had diffuse hyperplastic goiters and were selected to receive estrogen therapy either because of extreme toxicity or because they had shown no improvement following the usual preoperative preparation. In each case, subtotal thyroidectomy was performed by the same surgeon (A. H. S.). In three cases the operation was done in a single stage, while in two cases a two-stage operation was performed. Two of the patients had received iodine elsewhere for some time preceding hospital admission, and were considered to be iodine-fast. In addition to estrogen therapy, preoperative preparation included bed rest; Lugol's solution, minims 10 to 15 t.i.d.; sodium bromide sedation; a high calorie diet; calcium gluconate, gr. 15 t.i.d.; and large doses of vitamins A, B<sub>1</sub>, or B complex, C, and D. Three of the patients had a fulminating type of hyperthyroidism. The average basal metabolic rate in estrogen-treated cases was +57 per cent (Fig. 1). The average pulse rate on admission was 114 beats per minute (Fig. 4). Of the five patients, four were females.

*Control Cases.*—Seven patients with hyperthyroidism who received the same basic preoperative treatment, with the exception of estrogen therapy, and who were operated upon by the same surgeon (A. H. S.), have been studied and constitute a basis for the comparison shown in the accompanying graph. Of these patients, three had diffuse hyperplastic goiters, and four had nodular goiters. The average basal metabolic rate in the control group was +41 per cent (Fig. 1) and the average pulse rate on admission in the control cases was 102 beats per minute (Fig. 4).

*Estrogenic Substances Used, Including the Amounts and Methods of Administration.*—The estrogenic substances used were theelin in oil administered intramuscularly, supplemented in one case by diethylstilbestrol, administered by mouth. On account of uncertainty concerning the effects of estrogenic substances when administered to patients with hyperthyroidism, the doses in the first cases were small, as indicated in the following summary.

CASE 1.—Doses of 2,000 estrogenic units of theelin in oil were administered daily for six days preceding operation.

CASE 2.—In this case, thyroidectomy was done in two stages. Doses of 10,000 estrogenic units of theelin in oil were administered on the day preceding the first stage. Preceding the second stage, 10,000 estrogenic unit doses of theelin in oil were administered for three days.

CASE 3.—This patient received theelin in oil, 10,000 estrogenic units daily, for two days preceding operation.

CASE 4.—Theelin in oil, 10,000 estrogenic units, was administered daily for three days preceding operation.



Fig. 1.—Graphic representation of the average basal metabolic rates on admission of the control cases, and of those selected to receive estrogenic substances. The higher average metabolic rate in the latter group was paralleled by signs and symptoms of greater toxicity.

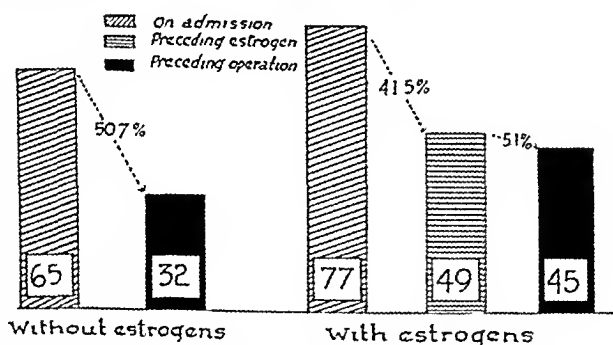


Fig. 2.—Chart showing the reduction in the average basal metabolic rate during the preoperative period in the three most toxic patients in the control group, compared with that in the three most toxic patients who received estrogen therapy.

CASE 5.—In this case operation was done in two stages. Theelin in oil, 10,000 estrogenic units, was administered daily for two days preceding the first stage. Following the first stage, 4 mg. of diethylstilbestrol were given by mouth during the first twenty-four hours following operation, and 1 mg. was given during the second twenty-four-hour postoperative period. Theelin in oil, 10,000 estrogenic units, was also administered daily for two days preceding the second-stage operation.

*Results.*—Fig. 2, which is based on the three most toxic cases in the group receiving estrogen therapy, and on the three most toxic cases in the control group, shows the comparative reductions in the average basal metabolic rate during the preoperative periods in the control cases and the cases which were selected to receive estrogen therapy. The refractoriness to usual preoperative therapy in the latter group is clearly shown, and the additional lowering of basal metabolic rate following estrogen therapy, although not great, may be considered to be somewhat significant.

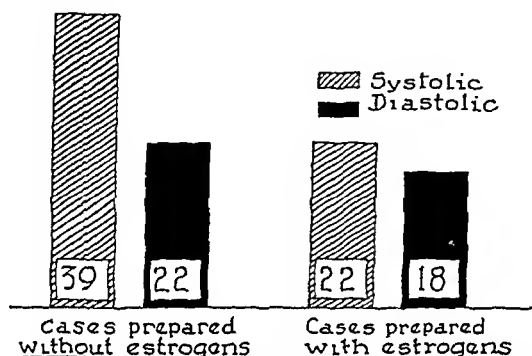


Fig. 3.—Chart showing the average variations in blood pressures during operation in those patients who received only ordinary preoperative preparation, compared with those patients who also received estrogenic substances.

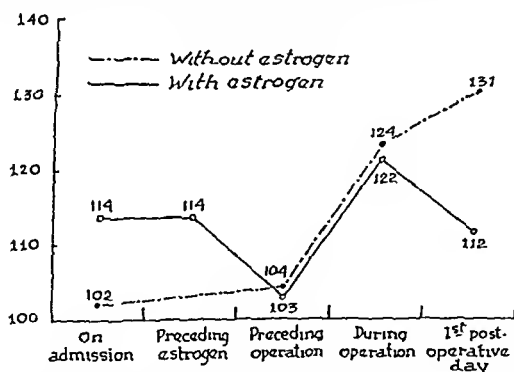


Fig. 4.—Graph showing average pulse rates in the estrogen-treated cases compared with those in the control group, on admission, in response to preoperative treatment, during operation, and on the first postoperative day.

The average variations in blood pressures during operation are shown graphically in Fig. 3, which demonstrates that fluctuations in both systolic and diastolic blood pressures during operation were less in the estrogen-prepared group of cases.

The average pulse rates in the estrogen-treated cases compared with those in the control group at the time of admission, in response to preoperative treatment, during operation, and on the first postoperative day, is indicated in Fig. 4. Although the average pulse rate in the cases

which received estrogen therapy remained elevated following the basic treatment employed in all cases, the administration of estrogen was followed by a fall in pulse rate to approximately the same level reached by the less toxic control cases. Whereas the average pulse rate during operation was practically the same in both the estrogen-treated and control groups, the average pulse rate on the first postoperative day was much lower in the cases which received estrogens.

In addition to the graphic demonstrations of the favorable effects apparently produced by estrogen therapy, as shown in Figs. 2, 3, and 4, other objective evidences of beneficial effects of estrogen therapy included improvement in respect to nervousness, apprehensiveness, and purposeless movements. Accompanying subjective improvement was evidenced by the greater feeling of well-being experienced by the estrogen-treated patients during the preoperative period. Furthermore, the postoperative courses of the patients treated with estrogens were remarkably smooth.

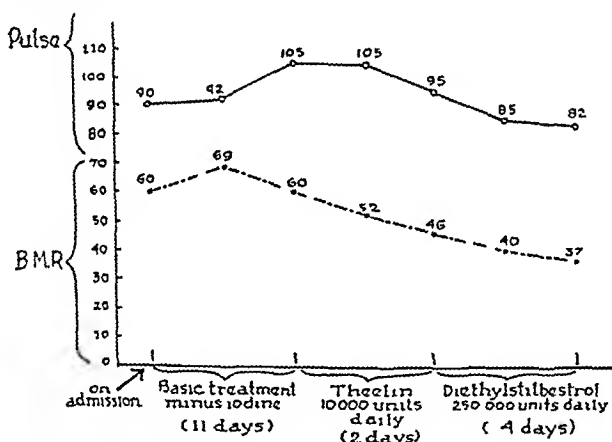


Fig 5—Graph showing the changes in basal metabolic rates and pulse rates, in a patient not included in the present comparative analysis, following the administration of relatively large doses of estrogens. Continued administration of diethylstilbestrol for a period shown in this graph was associated with a rise in the pulse rate, refractoriness to estrogen therapy may occur. This pulse, and the subtotal thyroidectomy which was later done was followed by an uneventful recovery.

#### DISCUSSION

Because of the uncertainty of the effect of estrogen therapy in spontaneous hyperthyroidism in the human being, there was considerable variation in the amount and the timing of the doses of estrogenic substances. After observing the apparent benefit and the absence of undesirable reactions when small doses were administered, larger doses were subsequently employed. In this small group of cases it was impossible to establish any significant relationships between the amounts of estrogenic substances administered and the beneficial effects observed.

Further observations are presently in progress concerning the effect of diethylstilbestrol and monomethylstilbestrol given in various amounts and according to different dose schedules. Fig. 5 shows the changes in basal metabolic rates and pulse rates, in a patient not included in the present comparative analysis, following the administration of relatively large doses of estrogens. Continued administration of diethylstilbestrol for several days following the period shown in this graph was associated with a rise in the rates, suggesting that refractoriness to estrogen therapy may occur. This patient was subsequently given iodine, and the subtotal thyroidectomy which was later done was followed by an uneventful recovery.

### CONCLUSIONS

From observations in a small group of cases with hyperthyroidism, selected either because of their failure to respond to the usual preoperative preparation, or because of the severity of the disease, the administration of estrogenic substances in conjunction with both single and two-stage thyroidectomies appears to be beneficial.

### REFERENCES

1. Storek, Ambrose H.: Discussion of Starr, Paul, and Davis, Loyal: Endocrine Studies of Patients After Subtotal Hypophysectomy, *Tr. South. S. A.* 53: 137, 1940.
2. Sherwood, T. C., and Bowers, L. M.: The Effect of Ovarian Hormone on the Basal Metabolism of Experimental Hyperthyroid Rats, *Am. J. Physiol.* 115: 645, 1936.
3. Grumbrecht, P., and Loeser, A.: Quoted by Sherwood.<sup>35</sup>
4. Smith, M. G., and Moore, E.: Is Anterior Pituitary Hormone Demonstrable in Urine of Graves' Disease, in Urine of Guinea Pigs Injected With Anterior Pituitary Extract? *Proc. Soc. Exper. Biol. & Med.* 30: 735, 1933.
5. Krogh, Marie, and Okkels, H.: L'hormone thyroïdostimulante préhypophysaire est-elle présente dans l'urine? *Compt. rend. Soc. de biol.* 113: 635, 1933.
6. Hertz, Saul, and Oastler, E. G.: Assay of Blood and Urine for Thyrotropic Hormone in Thyrotoxicosis and Myxedema, *Endocrinology* 20: 520, 1936.
7. Antognetti, L., and Gerioli, F.: Studi sui "Tests" ormonici, cited by Collip, J. B.: *J. A. M. A.* 115: 2073, 1940.
8. Bodart, F., and Fellinger, K.: Ueber die thyreotrope Wirkung des Serums bei endocrinen Erkrankungen, cited by Collip, J. B.: *J. A. M. A.* 115: 2073, 1940.
9. Emerson, Kendall, Jr., and Cutting, W. C.: Urinary Thyrotropic Hormone, *Endocrinology* 23: 439, 1938.
10. Rawson, R. W., and Starr, Paul: Direct Measurement of Height of Thyroid Epithelium; a Method of Assay of Thyrotropic Substance; Clinical Application, *Arch. Int. Med.* 61: 726, 1938.
11. Sendrail, M., and Tamalet, L. J.: Le test hypophysaire d'Aron en clinique, cited by Collip, J. B.: *J. A. M. A.* 115: 2073, 1940.
12. Howell, L. P.: The Excretion of Gonadotropic Principle in Thyroid Disease, *Tr. Am. A. Study Goiter*, p. 157, 1940.
13. Starr, Paul, and Patton, Helen: Studies of Variations in Individual Human Response to Thyrotropic Hormone Preparations, *Tr. Am. A. Study Goiter*, p. 150, 1940.
14. Sherwood, T. C.: Effect of Estrogenic Substance on Experimentally Hyperthyroid Male Rats, *Endocrinology* 29: 215, 1941.
15. Schneider, E., and Widmann, E.: *Klinische und experimentelle Untersuchungen zum Problem des Kropfes und der Basedowschen Krankheit*, cited by Collip, J. B.: *J. A. M. A.* 115: 2073, 1940.
16. Billingsley, L. W., O'Donovan, D. K., and Collip, J. B.: The Specific Metabolic Principle of the Pituitary, *Endocrinology* 24: 63, 1939.

17. O'Donovan, D. K., and Collip, J. B.: The Specific Metabolic Principle of the Pituitary and Its Relation to the Melanophore Hormone, *Endocrinology* 23: 718, 1938.
18. Houssay, B. A., and Artundo, A.: Action de l'extrait Anté-hypophysaire sur le Métabolisme Basal des Chiens Hypophysoprives et Thyroprives. Quoted by Collip et al.<sup>22</sup>
19. Gaebler, O. H.: Some Effects of Anterior Pituitary Extracts on Nitrogen Metabolism, Water Balance, and Energy Metabolism, *J. Exper. Med.* 57: 349, 1933.
20. Gaebler, O. H.: Effects of Thyroparathyroidectomy and Carbohydrate Intake on the Action of Anterior Pituitary Extracts, *Am. J. Physiol.* 110: 584, 1935.
21. Riddle, O., Smith, G. C., Bates, R. W., Moran, C. S., and Lahr, E. L.: Action of Anterior Pituitary Hormones on Basal Metabolism of Normal and Hypophysectomized Pigeons and on a Paradoxical Influence of Temperature, *Endocrinology* 20: 1, 1936.
22. Collip, J. B., Neufeld, A. H., and Denstedt, O. F.: The Specific Metabolic Factor of the Pituitary, *Tr. Am. A. Study Goiter*, p. 219, 1939.
23. Rogowitsch, N.: Veränderungen der Hypophyse nach Entfernung der Schilddrüse, cited by Lerman, Jacob: *J. A. M. A.* 117: 349, 1941.
24. Smith, P. E.: Experimental Ablation of the Hypophysis in the Frog Embryo, *Science* 44: 280, 1916.
25. Uhlenhuth, Eduard: The Thyreoactivator Hormone, Its Isolation From the Anterior Lobe of the Bovine Pituitary Gland, and Its Effects on the Thyroid Gland, *Tr. Am. A. Study Goiter*, p. 25, 1936.
26. Shoenkaert, J. A.: Hyperplasia of Thyroid and Exophthalmus From Treatment With Anterior Pituitary in Young Duck, *Proc. Soc. Exper. Biol. & Med.* 29: 306, 1931.
27. Krogh, Marie, and Okkels, Harald: Sur l'histophysiologie du corps thyroïde, Stades initiaux de la sécrétion thyroïdienne, *Compt. rend. Soc. de biol.* 112: 1694, 1933.
28. Eitel, Herman, Krebs, H. A., and Loeser, Arnold: Hypophysenvorderlappen und Schilddrüse: Die Wirkung der thyreotropen Substanz des Hypophysenvorderlappens auf die Schilddrüse in vitro, cited by Collip, J. B.: *J. A. M. A.* 115: 2073, 1940.
29. Marine, David: Physiology and Principal Interrelations of the Thyroid, *J. A. M. A.* 104: 2250, 1935.
30. Friedgood, H. B.: Similarity of the Iodin Remission in Experimental Anterior Hypophyseal Hyperthyroidism, the Hyperthyroidism of Acromegaly and That of Exophthalmic Goiter, *Endocrinology* 20: 526, 1936.
31. Thompson, W. O., Thompson, P. K., Taylor, S. G., III, and Dickie, L. F. N.: Interrelationships of Pituitary and Thyroid, *Tr. Am. A. Study Goiter*, p. 55, 1936.
32. Collip, J. B.: Properties of Anterior Lobe Extracts, Cold Spring Harbor Symposium on Quantitative Biology, Cold Spring Harbor, L. I., N. Y. 5: 210, 1937.
33. Williams, R. G.: Microscopic Studies of Living Thyroid Follicles Implanted in Transparent Chambers Installed in the Rabbit's Ear, *Am. J. Anat.* 62: 1, 1937.
34. Elmer, A. W.: The Etiology and Pathogenesis of Thyrotoxicosis, *New England J. Med.* 221: 927, 1939.
35. Means, J. H., Hertz, Saul, and Lerman, Jacob: The Pituitary Type of Myxedema or Simmonds' Disease Masquerading as Myxedema, *Tr. Am. A. Physicians* 55: 32, 1940.
36. Sherwood, T. C.: Relation of Estrogenic Substances to Thyroid Function and Respiration Metabolism, *Am. J. Physiol.* 124: 114, 1938.
37. Sherwood, T. C.: Effect of Stilbestrol on Basal Metabolism of Experimental Hyperthyroid Rats, *Endocrinology* 26: 693, 1940.
38. Sherwood, T. C.: Further Studies on Ovarian Thyroid Relationship, *Endocrinology* 27: 925, 1940.



# SKELETAL MANIFESTATIONS OF THYROID DISEASE

MILTON BODENHEIMER, M.D., AND IRVING S. BARCHAM, M.D.,  
NEW YORK, N. Y.

*(From the Surgical Services of the Hospital for Joint Diseases)*

**D**ISEASES of the thyroid gland not infrequently have skeletal manifestations of great significance. Neoplasms of thyroid origin, hypo- and hyperthyroidism are commonly associated with changes in the osseous structures, which, however, are not often recognized clinically, except in those cases of bone metastases from carcinoma of the gland. A review of the literature and a description of six cases which we have observed have been undertaken in order to illustrate the various changes.

## NEOPLASMS

Neoplasms of the thyroid gland may arise from any of the germinal layers. Mesenchymal tumors are quite rare. Those arising from the endothelium are the most common. According to Simpson, 4 per cent of all goiters without exophthalmos are carcinoma. In a series of 238 cases of carcinoma of the thyroid, Erhardt<sup>8</sup> found the following metastatic distribution: lung, 129; bones, 66; liver, 36; kidneys, 20; pleura, 16; and brain, 12. The order of frequency of bone involvement was: skull, vertebrae, pelvis, sternum, and femur.

Thyroid tissue has been found in almost every bone of the body. It consists of tissue which has the microscopic anatomy of normal fetal or adult thyroid gland, some appearing benign and others malignant. In either case it is easily demonstrated that the thyroid struma has invaded normal bone structure and replaced it by first destroying it. In cases where malignancy is found, the primary focus is usually found in a carcinomatous thyroid gland. This type of case is easily diagnosed and causes little confusion. The involved bone presents rarefied areas at the sites of metastases on roentgenograms.

**CASE 1** (Hosp. No. 61672).—O. F., a 34-year-old white male, was admitted on Nov. 11, 1936, with the chief complaint of sudden, sharp, stabbing pain in the anterior neck, aggravated by deep breathing and associated with dyspnea. He also complained of pain above the right eye. The total duration of the complaints was four months. One year previous to this admission the patient had been at another hospital from which a report indicated that he had had a partial resection of a carcinoma of the thyroid because of pressure symptoms. Pulmonary metastasis had been demonstrated at that time. During this admission roentgenograms showed involvement of the right upper lobe of the lungs and three rarefied areas of the parietal bone along the vertex (Fig. 1). On Dec. 5, 1936, the patient was discharged unimproved. No follow-up was obtainable.

**CASE 2** (Hosp. No. 58253).—R. S., a 65-year-old white female, entered the Hospital for Joint Diseases on April 13, 1936, because of weakness and a mass

in the neck which she had had for fifteen years. The thyroid was replaced by a very hard mass, approximately 10 cm. by 6 cm., extending under the right sternomastoid muscle and adherent to it. X-rays showed two metastatic deposits in the right middle lobe of the lung. Basal metabolic rate was plus 15 per cent.

Because of pressure symptoms on the trachea, the mass was removed on April 25, 1936. The patient failed steadily after operation and died May 3, 1936, eight days after operation, from cardiovascular failure. Postmortem examination revealed an anaplastic carcinoma of the thyroid gland which had metastasized to the lungs, pleura, pericardium, hilar lymph nodes, and sternum. The metastasis to bone showed the typical replacement by destruction.

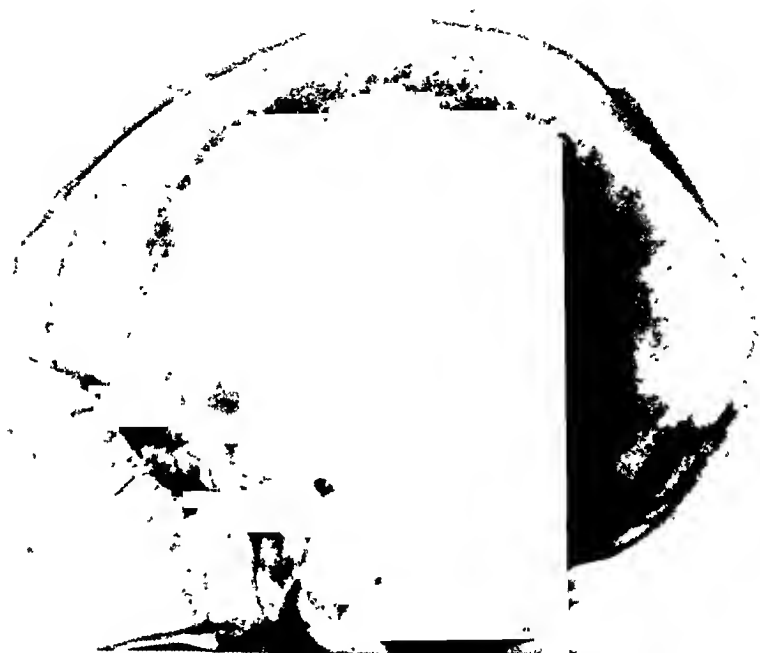


Fig. 1—Patient O. F. Arrows indicate osteoporotic areas in the parietal bone.

The situation becomes increasingly complicated where thyroid tissue is found in bone without any evidence, clinically, of involvement of the thyroid gland itself. The pathology of replacement by bone destruction is the same as presented in the preceding cases. This group of cases may be subdivided into two types: (1) benign, and (2) malignant. The benign lesion is considered by some authorities to consist of aberrant thyroid tissue from misplaced embryonic rests. The malignant group may be further classified into: (1) malignant degeneration of aberrant thyroid tissue, and (2) metastasis from a thyroid gland which has at some time borne a carcinoma.

"Benign" thyroid neoplasms in bone may be aberrant misplacements or "benign" metastases, capable of assuming malignant potentialities. This is still a heated point of controversy. Pathologic reports

by Douglas Symmers from two cases described by Kaplan<sup>10</sup> demonstrate the first theory. Symmers believes that aberrant thyroid tissue may be found in regions away from the head and neck. In the first case the pathologic report reads: "Thyroid tissue showing in places rather high alveolar epithelium . . . otherwise thyroid shows no noteworthy histological changes from the normal. There is nothing in the tissue to suggest malignancy. It undoubtedly represents aberrant thyroid tissue such as has not infrequently been described in various parts of the body including the meninges." In the second case Symmers reported: "Microscopic examination shows the presence of characteristic thyroid tissue . . . in other words, the histology of the mass . . . shows the presence of thyroid tissue which does not depart noticeably from that picture which perhaps might be considered normal. There is certainly nothing whatsoever in the tissue to indicate histologically any sign of malignant transformation. In other words, it seems to be an established fact that there are those growths which are histologically benign but which nevertheless are capable of malignant behavior in that they set up secondary deposits in distant structures." Cruickshank<sup>5</sup> favors the theory of benign metastasis and we quote from his writings: "A normal thyroid, a colloid thyroid, a thyroid containing a small adenoma, a thyroid containing a malignant adenoma, each has at some time or the other been reported as having produced a metastasis consisting of normal thyroid tissue. The clinical fact or observation remains that tumors identical with normal thyroid tissue do occur in bones of patients who present no apparent abnormality of their thyroid glands."

The most recent explanation of these diverse findings has been offered by I. Levin.<sup>11</sup> He concludes that there is either a favorable or an unfavorable medium for growth of cancer cells and that bone is a good medium. Normal thyroid tissue, however, is relatively resistant to growth of cancer cells. It is for this reason that the paradox of thyroid tumor metastasis to bone exists with no evidence of malignancy in the thyroid itself. Furthermore, so-called aberrant thyroid tissue existing as a metastatic deposit from a thyroid neoplasm, may assume malignant potentialities when located in a good "culture medium" such as bone.

Whenever a rarefying bone lesion is found, other diagnostic possibilities in addition to thyroid neoplasms also arise. Multiple myeloma, endothelioma, and hyperparathyroidism may produce a similar picture. The distinguishing differential points are to be found in the accompanying table.

One other characteristic sometimes found in thyroid deposits in bone should be borne in mind. Several cases of pulsating tumors over bony regions have been reported in the literature with thyroid neoplasm as the culprit.<sup>4</sup> To make a preoperative diagnosis in these cases is extremely difficult since the lesion more frequently resembles an aneurysm,

TABLE I

DISEASE	SYMPTOMS	BONES INVOLVED	X-RAY	BENCE-JONES	BLOOD CA., P.	PHOSPHATASE	CA., P. BALANCE
Thyroid tumors	Pain	Ribs, spine, skull, femur, humerus	Destruction with no new growth. Pathologic fracture may occur	Positive if marrow involved	Normal	Usually high	Normal
Multiple myeloma	Pain	Multiplicity of flat bones, as a rule	Small circumscribed lesions. Rarefaction; thinning of cortex	Positive	Normal	Normal	Normal
Endothelioma	Pain	Multiplicity and all bones may be involved	Peculiar longitudinal striated appearance of shaft with signs of invasion and no bone formation	Negative	Normal	Normal	Normal
Hyperparathyroidism	Pain in supporting bones. Hypotonia, nausea, vomiting, cramps. Polyuria, polydipsia due to increased excretion of Ca. and P.	Long tubular bones, pelvis, skull, jaw, ribs	<i>Early:</i> osteoporosis in medulla and beneath periosteum. Also bowing, exostoses, flattening of pelvis, miliary granular type of osteoporosis	Negative	High Ca. Low P.	High	Negative balance

an angioma, a meningocele, a hematoma, or some other highly vascular tumor.<sup>4</sup> In 1930 Wilkens<sup>20</sup> reported a patient who he first thought had an arteriovenous aneurysm. Frozen section at the time of the operation showed tissue not unlike fetal adenoma of the thyroid. Cruickshank<sup>5</sup> in 1938 presented another case of pulsating tumor due to thyroid metastasis to bone. The preoperative diagnosis was meningocele. The postoperative diagnosis was gumma or sarcoma. Pathologic examination was necessary in order to make a final diagnosis.

The differential diagnosis of pulsating tumors revolves about two important points: (1) a decision must be made as to whether the lesion is benign or malignant, and (2) the absence of a thyroid lesion or a long interval of many years between an excised thyroid gland neoplasm and a pulsating tumor of bone may be misleading.

Aneurysms or angiomata show slow clinical progress. The progression of symptoms in malignant, pulsating, metastatic thyroid lesions of bone is rather rapid. In the latter, roentgenographic evidence of bone destruction and the rapid development of neurologic signs are much more common. The diagnosis is finally confirmed by exploration and histologic examination.

It has also been said<sup>8</sup> that 50 per cent of thyroid metastatic bone malignancies have symptoms of hyperthyroidism. Removal of the primary lesion rarely produces changes in the symptoms but removal of the secondary growth might give rise to myxedema.

Our third case report is very interesting since it combines a number of illustrations of the features already brought forth. It demonstrates the long interval between primary and secondary lesion; it is illustrative of the controversial arguments as to the origin of the secondary lesion; it demonstrates pulsating tumors of thyroid metastatic origin with differential features of diagnosis; it shows hyperthyroidism as a result of thyroid metastatic deposit in bone, since removal of the secondary lesion gave marked relief from thyrotoxic symptomatology.

CASE 3 (Hosp. No. 79401).—B. B., a 45-year-old white male, was admitted to the Hospital for Joint Diseases on three different occasions. His first admission, in 1938, was for pain in the right shoulder, which was diagnosed as arthritis and treated by immobilization. In 1939 he was admitted for symptoms of hyperthyroidism, notably tremor, weakness, and loss of weight. At that time he stated that he had had a thyroidectomy in 1923 at a Cleveland hospital because of "over active goiter." The left lobe of the thyroid was apparently enlarged and basal metabolic rate was plus 24 per cent. He was given medical treatment for hyperthyroidism and discharged, four weeks later, improved and with basal metabolic rate plus 10 per cent.

In October, 1939, he returned to the hospital complaining of severe pain in the lower back radiating to the lower extremities. Onset was sudden, one week previously, and progression of the intensity of pain was rapid. His symptoms of hyperthyroidism had also recurred and become marked. The striking feature of the physical examination was the presence of a mass in the region of the spinous

processes of the eleventh and twelfth dorsal vertebrae (Fig. 2). The tumor measured about 4 cm. in diameter and pulsated synchronously with each cardiac systole. Radiographs showed an absence of the spinous process of the eleventh dorsal vertebra (Fig. 3) and of the descending articular process of the twelfth dorsal vertebra (Fig. 4). Other x-rays of the spine, after injection of opaque fluid, demonstrated a midline tumor which was highly vascular and encroached on the spinal canal.



Fig. 2—Patient B. B. Photograph of patient showing the location of the pulsating tumor.



Fig. 3—Patient B. B. Roentgenogram showing absence of spinous process of the eleventh dorsal vertebra.

Two basal metabolic rates were plus 27 per cent and plus 46 per cent. The fasting blood sugar was 89 mg. per cent, the serum calcium 10.6 mg. per cent, the serum phosphorus 3.3 mg. per cent. The serum phosphatase was elevated to

an angioma, a meningocele, a hematoma, or some other highly vascular tumor.<sup>4</sup> In 1930 Wilkens<sup>20</sup> reported a patient who he first thought had an arteriovenous aneurysm. Frozen section at the time of the operation showed tissue not unlike fetal adenoma of the thyroid. Cruickshank<sup>5</sup> in 1938 presented another case of pulsating tumor due to thyroid metastasis to bone. The preoperative diagnosis was meningocele. The postoperative diagnosis was gumma or sarcoma. Pathologic examination was necessary in order to make a final diagnosis.

The differential diagnosis of pulsating tumors revolves about two important points: (1) a decision must be made as to whether the lesion is benign or malignant, and (2) the absence of a thyroid lesion or a long interval of many years between an excised thyroid gland neoplasm and a pulsating tumor of bone may be misleading.

Aneurysms or angiomata show slow clinical progress. The progression of symptoms in malignant, pulsating, metastatic thyroid lesions of bone is rather rapid. In the latter, roentgenographic evidence of bone destruction and the rapid development of neurologic signs are much more common. The diagnosis is finally confirmed by exploration and histologic examination.

It has also been said<sup>8</sup> that 50 per cent of thyroid metastatic bone malignancies have symptoms of hyperthyroidism. Removal of the primary lesion rarely produces changes in the symptoms but removal of the secondary growth might give rise to myxedema.

Our third case report is very interesting since it combines a number of illustrations of the features already brought forth. It demonstrates the long interval between primary and secondary lesion; it is illustrative of the controversial arguments as to the origin of the secondary lesion; it demonstrates pulsating tumors of thyroid metastatic origin with differential features of diagnosis; it shows hyperthyroidism as a result of thyroid metastatic deposit in bone, since removal of the secondary lesion gave marked relief from thyrotoxic symptomatology.

CASE 3 (Hosp. No. 79401).—B. B., a 45-year-old white male, was admitted to the Hospital for Joint Diseases on three different occasions. His first admission, in 1938, was for pain in the right shoulder, which was diagnosed as arthritis and treated by immobilization. In 1939 he was admitted for symptoms of hyperthyroidism, notably tremor, weakness, and loss of weight. At that time he stated that he had had a thyroidectomy in 1923 at a Cleveland hospital because of "over active goiter." The left lobe of the thyroid was apparently enlarged and basal metabolic rate was plus 24 per cent. He was given medical treatment for hyperthyroidism and discharged, four weeks later, improved and with basal metabolic rate plus 10 per cent.

In October, 1939, he returned to the hospital complaining of severe pain in the lower back radiating to the lower extremities. Onset was sudden, one week previously, and progression of the intensity of pain was rapid. His symptoms of hyperthyroidism had also recurred and become marked. The striking feature of the physical examination was the presence of a mass in t

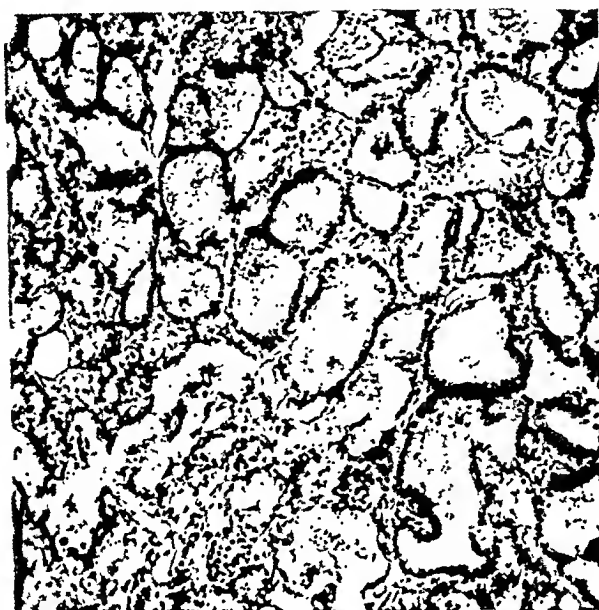


Fig. 5.—Patient B. B. Low power microphotograph of the tumor. This shows the papilliferous nature of the adenocarcinoma with the tendency toward formation of thyroid acini.

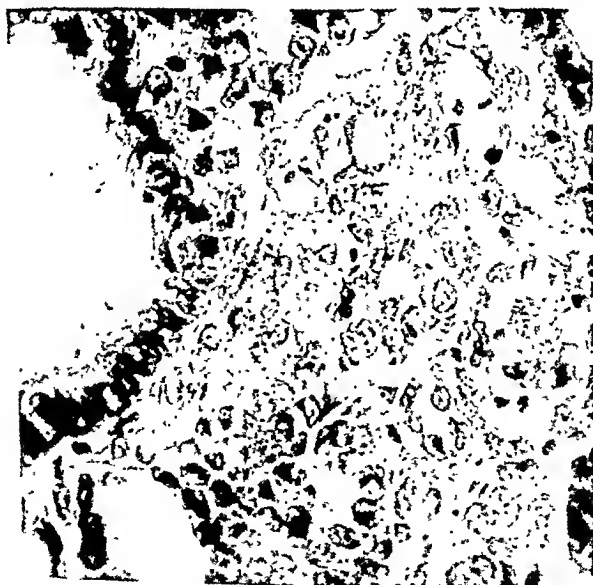


Fig. 6.—Patient B. B. High power magnification showing invasion of connective tissue by carcinoma cells.



9.9 Bodansky units. The urinary Bence-Jones reaction was negative. The provisional preoperative diagnosis was an aneurysm.

Ono observer palpated a firm hard nodule in the left sternomastoid muscle. He was of the opinion that this might be the primary site of the neoplasm producing a metastasis to the back. Other diagnoses were osteolytic sarcoma and hemangioma.

11 D  
ARTICULAR  
PROCESS

12 D  
PROCESS  
ABSENT

Fig. 4.—Patient B. B. Lateral roentgenogram showing the absence of the descending articular facet of the twelfth dorsal vertebra.

On Nov. 9, 1940, an exploratory operation was performed. A circular tumor about 3.5 cm. in diameter was found deep in the fascia. It completely destroyed the spinous process of the eleventh dorsal vertebra. The entire tumor together with the laminae of the twelfth dorsal and the first lumbar vertebrae were removed. It was then seen that the tumor did not involve the dura. Pulsations were noted, but so far as could be determined, they seemed to be transmitted to the tumor from the deeper structures. The exact nature of the tumor could not be determined at that time. The diagnosis, therefore, remained in doubt until the histologic examination was completed. This showed numerous areas of thyroid tissue with replacement by papilliferous adenocarcinoma (Figs. 5 and 6). This diagnosis was substantiated by a later report from the St. Vincent's Charity Hospital of Cleveland, which indicated that at the time of the thyroidectomy in 1923 a malignant adenoma had been found.

skeletal change is very difficult. Nevertheless, skeletal disease unaccounted for except by the presence of hypothyroidism may be deemed to be a resultant of a combination of forces in a generalized disordered metabolic process. The pathology consists of a lack of replacement of resorbed bone by osteoid tissue and its ossification, just as cells of any soft tissue replace those which die. The following report presents a patient with severe skeletal changes in whom an exhaustive investigation revealed only a hypothyroid state. This patient did not respond to orthopedic management alone, but a period of thyroid management produced a satisfactory response.



Fig. 8.—Patient M. D. Roentgenograms of the dorsal spine in the interoposterior view showing compression of the bodies of the sixth, seventh, and eighth dorsal vertebrae.

CASE 1 (Hosp. No. 73053).—M. D., aged 46 years, was admitted on Dec. 9, 1918, with a five week history of pain in the back, "crushing and tearing" in character. The significant finding on physical examination was the patient's pos-

The mass noted in the sternomastoid muscle was removed but showed no thyroid tumor nor evidence of adenocarcinoma. The patient's further course was uneventful and the hyperthyroid symptoms lessened. When last seen in October, 1940, there was no recurrence.

#### HYPOTHYROIDISM

Skeletal changes of hypothyroidism are of three main varieties: (1) deficient growth in the young due to absence of, or retardation in, centers of ossification; (2) retardation of osteoid tissue replacement and ossification in adults; and (3) abnormal changes in the epiphyseal plate and epiphyses (juvenile chondroepiphysitis). The first group is not being considered in this review.

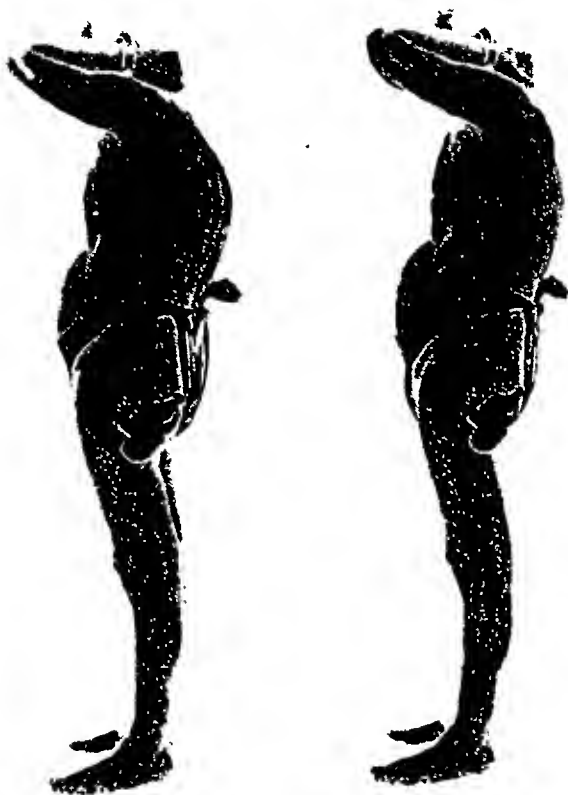


Fig. 7.—Patient M. D. Photograph showing the curve of the back with gibbus formation.

It has been commonly believed that when hypothyroid changes have their inception in adult life no skeletal changes result. This is true in a large majority of cases. However, hypothyroidism is manifested by a generalized metabolic disorder in which all of the endocrines play an important part. To absolutely link such hypothyroidism to any

skeletal change is very difficult. Nevertheless, skeletal disease unaccounted for except by the presence of hypothyroidism may be deemed to be a resultant of a combination of forces in a generalized disordered metabolic process. The pathology consists of a lack of replacement of resorbed bone by osteoid tissue and its ossification, just as cells of any soft tissue replace those which die. The following report presents a patient with severe skeletal changes in whom an exhaustive investigation revealed only a hypothyroid state. This patient did not respond to orthopedic management alone, but a period of thyroid management produced a satisfactory response.



FIG. 8.—Patient M. D. Roentgenograms of the dorsal spine in the anteroposterior view showing compression of the bodies of the sixth, seventh, and eighth dorsal vertebrae.

CASE 4 (Hosp. No. 73953).—M. D., aged 16 years, was admitted on Dec. 9, 1928, with a five week history of pain in the back, "crushing and tearing" in character. The significant finding on physical examination was the patient's pos

ture, which was notable for the sweeping flexion curve along the entire spine, with the greatest curvature in the dorsal region and gradual gibbus formation at about the level of the ninth and tenth dorsal vertebrae (Fig. 7). Pain was pronounced on either flexion or extension of the spine. Radiographs revealed marked compression of the bodies of the sixth, seventh, and eighth dorsal vertebrae with widening of the intervertebral spaces (Figs. 8 and 9). Most significant was the absence of evidence of a destructive process. The skull plate presented a moderate degree of osteoporosis. X-ray interpretation was that of a disordered metabolic process.



Fig. 9.—Roentgenogram of the same portion of the spine as in Fig. 8, but in lateral view.

Bence-Jones reaction of the urine was negative; basal metabolic rates were minus 19 per cent and minus 21 per cent. Kahn reaction was negative. The blood cholesterol was slightly elevated at 210 mg. per cent. The serum calcium was 9.9 mg. per cent and the serum phosphorus 3.5 mg. per cent. The serum phosphatase was slightly elevated at 8.8 Bodansky units. The patient improved with orthopedic management of the back and the administration of whole thyroid substance. He was last seen in Sept., 1939, when he was permitted to discard his brace.

That group of hypothyroid cases in which epiphyseal manifestations are noted mainly at the hip joints is very important because of the difficulty in differentiation from Legg-Calvé-Perthes disease.

Läwen in 1909 made the first clinical report of Legg-Calvé-Perthes disease in a cretin. Since 1920, when Engelbach designated the X-ray as a diagnostic factor in hypothyroidism, more cases of juvenile chondroepiphysitis or hypothyroid stippled epiphyses have appeared in the literature. That hypothyroidism bore a significant pathogenic relationship to stippled epiphyses was ably attested by the studies of Schaefer, Strickroot, and Purcell<sup>17</sup> in 1939. Two hundred fifty-eight endocrinopathic children from 8 to 15 years of age and ninety-nine



Fig. 10.—Patient N. S. Roentgenogram of the pelvis showing bilateral stippled epiphyses.

normal children in the same age group were subjects. In the former group, evidence of chondroepiphysal disturbance was demonstrated in 35.2 per cent of the patients. Among these, all but six cases were definitely associated with hypothyroidism, and only two cases were symptomatic. In the control group only 7 per cent showed chondroepiphysitis. Follow-up has shown eight cases among the endocrinopathic group with a return to normal bone detail after thyroid treatment.

The pathologic changes<sup>16</sup> underlying this disease are of the greatest import if one is to understand fully the differentiating features from Legg-Calvé-Perthes disease. Two important changes are to be noted, one at the epiphyseal plate and the other in the epiphysis itself. In the former a layer of bone is formed consisting of bony trabeculae lying transverse to the long axis of bone. This layer was found by Langhans to be detectable not only histologically but also roentgenographically since it had sufficient density.<sup>16</sup> In the epiphysis there exists



Fig. 11.—Photograph of patient N. S.

from the earliest growth period a number of centers of bone growth or ossification which never coalesce and which are separated by an irregular abnormal type of cartilaginous structure. This is in direct contrast to the Legg-Calvé-Perthes epiphysis which prior to its diseased state consisted of an epiphysis with a single center of ossification from which normal bone growth advanced outwardly. When seen in the

later stages of both endocrine juvenile chondroepiphysitis and Legg-Calvé-Perthes disease, both epiphyses appear the same, since in the former necrosis has supervened on the abnormal cartilaginous structure, while in the latter multiple areas of aseptic necrosis are the feature of the pathology. In Legg-Calvé-Perthes disease the changes at the epiphyseal plate are not to be found.

With the above pathologic features well understood it is easier to consider the differential diagnosis. Hip involvement in hypothyroid stippled epiphysis is usually bilateral but unilateral in Legg-Calvé-Perthes disease. The presence of roentgenographie abnormalities in bones other than those about the hip, such as the knee and ankle, stamp

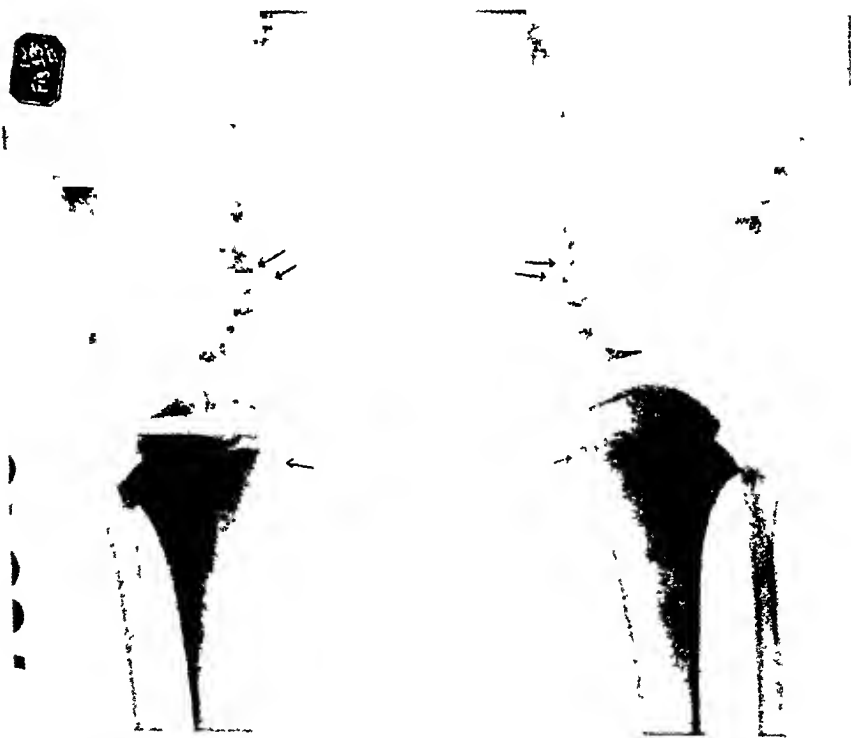


Fig. 12—Patient N. S. Roentgenogram of the knees with arrows indicating supracondylar osteoporotic bands.

the disease as endocrine in nature. No evidence of a destructive process is found in hypothyroid stippled epiphysis as is the case with Legg-Calvé-Perthes disease, although this feature is very often difficult to distinguish. Response to thyroid therapy is found usually in the endocrine group, whereas in Legg-Calvé-Perthes disease there is no such response. The following case report is one which illustrates the above features in great detail.



The pathologic changes<sup>16</sup> underlying this disease are of the greatest import if one is to understand fully the differentiating features from Legg-Calvé-Perthes disease. Two important changes are to be noted, one at the epiphyseal plate and the other in the epiphysis itself. In the former a layer of bone is formed consisting of bony trabeculae lying transverse to the long axis of bone. This layer was found by Langhans to be detectable not only histologically but also roentgenographically since it had sufficient density.<sup>16</sup> In the epiphysis there exists



Fig. 11.—Photograph of patient N. S.

from the earliest growth period a number of centers of bone growth or ossification which never coalesce and which are separated by an irregular abnormal type of cartilaginous structure. This is in direct contrast to the Legg-Calvé-Perthes epiphysis which prior to its diseased state consisted of an epiphysis with a single center of ossification from which normal bone growth advanced outwardly. When seen in the

In 1938 Bartels and Haggart<sup>2</sup> of the Lahey clinic reported two cases with compression fractures of the vertebrae, in both of whom clinical improvement was obtained after surgical treatment of the hyperthyroidism.

The skeletal manifestation of the disease is that of osteoporosis and any of its attending complications. The osteoporosis is generalized but appears earliest in the small flat bones and the spine and in the long bones latest. In 1929 Anb and his co-workers<sup>1</sup> demonstrated that the loss of calcium from bone was associated with a negative calcium metabolic balance. It has been shown<sup>1</sup> that whereas normal persons excrete 12.7 Gm. of calcium per kilogram of body weight over a three-day



Fig 14 —Patient N. S. Roentgenogram fifteen months after inception of treatment. Marked improvement to be noted in epiphyses

test period, patients with thyrotoxicosis eliminate 42 Gm. per kilogram of body weight. With the increase of calcium excretion phosphorus also shows a negative balance. When thyrotoxic patients manifesting calcium hyperexcretion were fed iodine, the calcium excretion returned to normal. The serum calcium and phosphorus remain normal. Increase in the serum phosphatase values was demonstrated by Hunter<sup>3</sup> but these values were only moderately high.

The negative calcium balance has no relationship to increase in basal metabolic rate, since comparable increases in metabolism occur in high fevers and leucemia without the concomitant excretion of large amounts

CASE 5 (Hosp. No. 82738).—N. S., a white male, aged 14 years, was admitted to the Hospital for Joint Diseases on Oct. 17, 1939, because of a left sided limp which had been present for 2½ years. X-rays revealed bilateral stippled epiphysis (Fig. 10) and the diagnosis of Legg Calve-Perthes disease was made. However, further study cast doubt on the diagnosis. A photograph of the patient resembled an individual of the hypothyroid-pituitary type (Fig. 11). Roentgenographs showed transverse supracondylar osteoporotic bands at the knee and ankle joints (Fig. 12). Other radiographic findings were slight thinning of the frontal bones, somewhat rudimentary and undeveloped sella turcica, and slight diminution in the vertical development of the long bones with increase in the widths of the shafts of the humeri.



Fig. 13.—Patient N. S. Roentgenogram nine months after the inception of treatment. Slight improvement in epiphyses to be noted

The basal metabolic rate was minus 2 per cent. Treatment was instituted. Both hips were immobilized and thyroid substitution therapy begun. In five months the patient had lost more than twenty pounds. Marked improvement of the epiphyses is to be noted progressively on roentgenograms taken in July, 1940 (Fig. 13), and Jan., 1941 (Fig. 14). The patient is still under treatment.

#### HYPERTHYROIDISM

The changes taking place in the osseous system as a result of hyperthyroidism are of a different type from those discussed above. The first case recognized roentgenographically was by Kummer in 1917.

gressed in spite of thyroidectomy. Means and co-workers<sup>13</sup> presented a patient with improvement of kyphosis and flaring of the ribs following thyroidectomy. Our patient disclosed roentgenographie improvement eight months following surgery.

The following case report illustrates the above facts. Calcium excretion determinations were not obtainable.

CASE 6 (Hosp. No. 79405).—J. I., a male negro 12 years of age, was admitted to the Pediatric Service Oct. 9, 1939, and later transferred to the Surgical service. For four years the patient had noticed an increased "popping" of his eyes. Nervousness, polyphagia, excessive perspiration, and loss of ten pounds in weight were noted during the year prior to this admission. The thyroid gland was symmetrically enlarged and soft; a bruit was heard on auscultation. The skin was warm and moist. Eye signs were; marked exophthalmos, lid lag, and widened palpebral fissures. There was a fine tremor of the tongue and hands. The pulse was forceful and its rate ranged in the vicinity of 140. The liver was moderately enlarged.



Fig. 16. Patient J. I. Roentgenogram of both hands. Marked osteoporosis of the phalanges and carpus to be noted.

Basal metabolic rate was plus 20 per cent. The serum calcium and phosphorus were within normal limits, being 10 mg. per cent and 5.3 mg per cent respectively. Both the cholesterol and cholesterol esters were diminished, 116 mg. per cent and 101 mg per cent respectively. The serum phosphatase was moderately elevated at 6.9 Bodansky units.

X ray examinations of the skeleton revealed moderate atrophy or decalcification of the bones of the knee joint (Fig. 15), the bones of the carpus and the hand (Fig. 16), the bones of the skull (Fig. 17), and the osseous structures of the

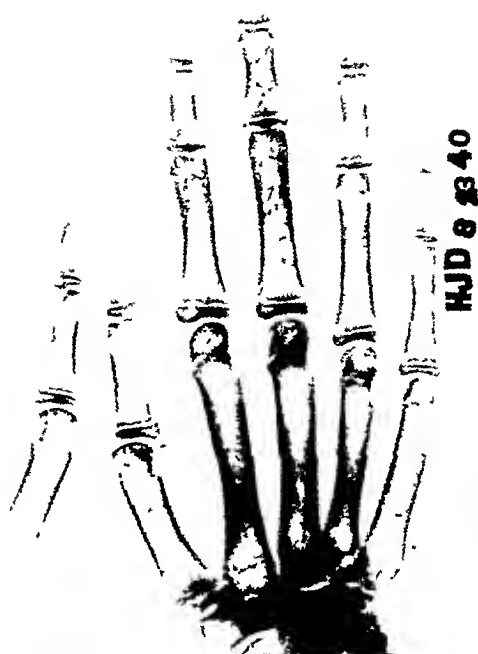
of calcium. The calcium excretion was shown<sup>1</sup> to be dependent upon three principal factors: (1) the duration of the disease, (2) the rate of calcium loss, and (3) the daily calcium intake. As to the etiology of the disease, it is the general consensus of opinion that the thyroid secretions play some part directly on the calcium deposits of bone. Mochlig and Adler<sup>14</sup> proposed the theory of an alteration in glycogen metabolism secondary to changes in the pituitary gland.



Fig. 15.—Patient J. I. Roentgenogram of the knee joints, marked osteoporosis to be noted.

It is interesting to note that in most of the cases reported, the disease was of five or more years' duration. In the two cases reported by Bartels and Haggart<sup>2</sup> the total duration was nine years in one case and seventeen years in the other case before bone changes were noted clinically. In the case herein presented there was a five-year history. It is therefore not surprising that in cases of hyperthyroidism of less than five years' duration no evidence of osteoporosis is demonstrable.

Little is reported on the results of surgical therapy in regard to the skeletal changes. In the first case of Bartels and Haggart<sup>2</sup> no bone recalcification was found one year after operation. In a case reported by Mochlig and Adler,<sup>14</sup> decalcification of vertebrae and pelvis pro-



rogram of the hand. After six months after operation  
terrible recalcification of the bones.



rogram of the leg. After six months after operation  
terrible recalcification.

shoulder joint. It is interesting to note that in this patient the areas of decreased calcification were most marked where the bone had been formed most recently, namely at the epiphyseal areas.

The patient was prepared with iodine therapy, during which time he gained ten pounds. A two-stage subtotal thyroidectomy was performed, with an eighteen-day interval between the stages. Pathology demonstrated hyperplastic thyroid with colloid involution. The postoperative course was uneventful and the patient made a good recovery. To date, follow-up in the outpatient department has shown no recurrence. The basal metabolic rate fifteen months following operation was plus 2 per cent. X-rays of the bones of the hands and the knees show a moderate degree of recalcification (Figs. 18 and 19).



Fig. 17.—Patient J. I. Roentgenogram of the skull, fairly marked degree of osteoporosis.

Another case, a female past the age of 50 years, was observed by one of us (M. B.). She sustained a fracture of the upper third of the humerus. The only history of trauma was a slight pull of the muscles. It was noted, however, that the patient had an exophthalmos which she stated had been present for about twenty years. There was no neck tumor. In addition to the fracture, radiographs disclosed osteoporosis of the long bones, the skull, and some segments of the spine. This was considered to be a case of "burned out" hyperthyroidism with osteoporosis.

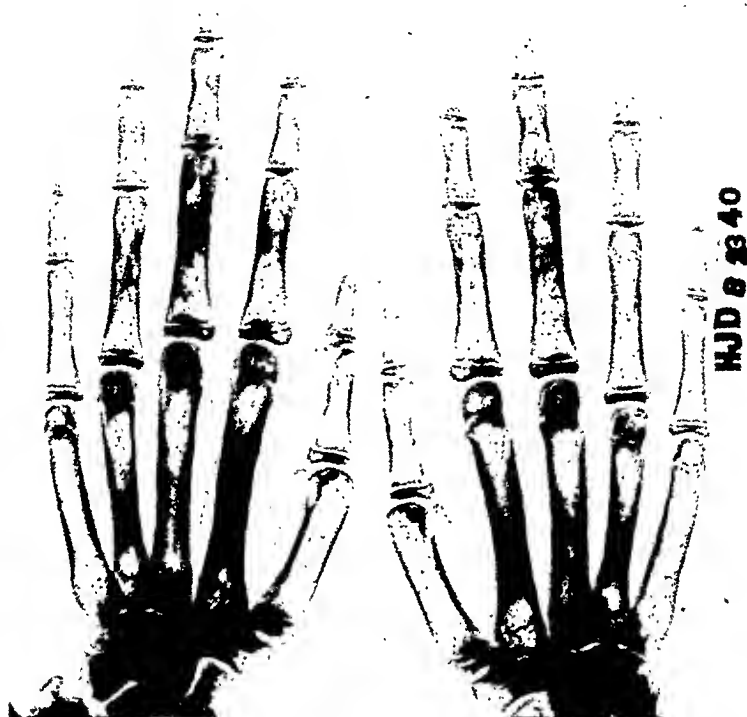


FIG. 18.—Patient J. I. Roentgenogram of the hands fifteen months after operation, showing considerable recalcification of the bones.



FIG. 19.—Patient J. I. Roentgenogram of the knee fifteen months after operation, showing recalcification.



## SUMMARY AND CONCLUSIONS

From the discussions above it can be realized that not infrequently a bone lesion is diagnosed without the relationship of thyroid disease having been recognized. Pulsating tumors may be diagnosed as aneurysm, hemangioma, meningocoele, or some other highly vascular tumor. The lesions are sometimes found on histologic examination to be secondary metastatic thyroid deposits occurring many years after the discovery of the primary lesion or even in the absence of any evidence of a primary lesion. Then again, the question of thyroid deposits in bone ever having been a metastasis or an aberrancy is still open. Bony lesions of thyroid origin also have simulated hyperparathyroid lesions, endothelioma, or multiple myeloma. Closer study reveals a differentiation.

Of all the skeletal manifestations of hypothyroidism perhaps the one most often unrecognized is stippled epiphyses of hypothyroidism. The characteristic pathologic changes of deficiency in centers of ossification, with irregularity of bone growth in addition to other characteristic changes at the epiphyseal plate, serve to differentiate this condition from Legg-Calvé-Perthes disease.

The osteoporotic changes of hyperthyroidism due to negative calcium balance are of great importance. Spontaneous fractures or fractures with little exciting cause have been reported in decalcified bones of a long-standing hyperthyroidism.

With thorough knowledge and understanding of the bone lesions described, treatment may be attempted on a more rational basis. Needling of so-called aneurysms of the spine will be attempted less often when one realizes that these lesions are often due to a thyroid metastasis. Thyroid substitution therapy in cases of stippled epiphyses is a great aid when definite evidence of hypothyroidism is established. Osteoporosis due to hyperthyroidism is sometimes benefited by thyroidectomy.

## REFERENCES

1. Aub, J. C., Bauer, W., Heath, C., and Roper, M.: Studies of Calcium and Phosphorous Metabolism: Effects of Thyroid Hormone and Thyroid Disease, *J. Clin. Investigation* 7: 97-137, 1929.
2. Bartels, E. C., and Haggart, G. E.: Osteoporosis in Hyperthyroidism, *New England J. Med.* 219: 373, 1938.
3. Benjamin, Bernard, and Miller, Philip: Hypothyroidism as a Cause of Disease of the Hip, *Am. J. Dis. Child.* 55: 1189, 1938.
4. Bodenheimer, M., and Bareham, I. S.: Pulsating Tumor Due to Thyroid Metastasis, *Bull. Hosp. Joint Dis.* 2: 20-27, 1941.
5. Cruickshank, M. M.: Thyroid Metastasis in Bone, *Indian M. Gaz.* 73: 656, 1938.
6. Dinsmore, Robert S., and Kicken, N. Fred: Metastasis From Malignant Tumors of the Thyroid; a Study of 124 Cases, *Am. J. Surg.* 24: 202, 1934.
7. Dunlop, H. F., and Moore, A. B.: Osteoporosis, Secondary to Hyperthyroidism, *M. Clin. North America* 12: 1511-1519, 1929.
8. Erhardt, Oscar: Die Anatomie und Klinik der Struma maligna, *Beitr. z. klin. Chir.* 35: 343, 1902.
9. Hunter, D.: Calcium and Phosphorous Metabolism, *Lancet* 1: 917-957, 1930.
10. Kaplan, Ira: Benign Metastatic Bone Involvement From Thyroid Tumors, *Am. J. Surg.* 23: 559, 1934.

11. Levin, Isaac: Skeletal Metastasis in Carcinoma of the Thyroid, *Am. J. Path.* 6: 563, 1930.
12. Lewin, P.: An Unusual Roentgenographic Finding in the Hip, *Am. J. Roentgenol.* 19: 290, 1928.
13. Means, J. H., Hertz, S., and Lerman, J.: Nutritional Factors in Graves Disease, *Ann. Int. Med.* 11: 429-436, 1937.
14. Moehlig, R. C., and Adler, S.: Carbohydrate Metabolism Disturbances and Results of Various Therapeutic Procedures, *Surg., Gynec. & Obst.* 64: 747-757, 1937.
15. Plummer, W. A.: Cases Showing Osteoporosis due to Decalcification in Exophthalmic Goiter, *Proc. Staff Meet., Mayo Clin.* 3: 119-121, 1928.
16. Reilly, Wm. A., and Smyth, Francis S.: Stippled Epiphyses With Congenital Hypothyroidism (Cretinoid Epiphyseal Dysgenesis), *Am. J. Roentgenol.* 40: 675, 1938.
17. Schaefer, Robert L., Strickroot, Fred L., and Purcell, Frank H.: The Endocrine Implication of Juvenile Chondroepiphysitis, *J. A. M. A.* 112: 1917, 1939.
18. Smith, E. E., and McLean, F. C.: Effect of Hyperthyroidism Upon Growth and Chemical Composition of Bone, *Endocrinology* 23: 546, 1938.
19. von Recklinghausen, F.: Die Fibrose oder deformirende Osteitis, die Osteomalacie und die osteoplastische Carcinose, in ihren gegenseitigen Beziehungen, *Festschrift für Rudolph Virchow, Berlin, 1891, George Reimer*, pp. 1-89.
20. Wilkens, Harry: Carcinoma of the Thyroid With Metastasis to the Skull, *J. Missouri M. A.* 27: 547, 1930.
21. Williamson, John: Thyroid Tumor With Multiple Metastasis, *Brit. J. Surg.* 24: 624, 1937.

## SUMMARY AND CONCLUSIONS

From the discussions above it can be realized that not infrequently a bone lesion is diagnosed without the relationship of thyroid disease having been recognized. Pulsating tumors may be diagnosed as aneurysm, hemangioma, meningocele, or some other highly vascular tumor. The lesions are sometimes found on histologic examination to be secondary metastatic thyroid deposits occurring many years after the discovery of the primary lesion or even in the absence of any evidence of a primary lesion. Then again, the question of thyroid deposits in bone ever having been a metastasis or an aberrancy is still open. Bony lesions of thyroid origin also have simulated hyperparathyroid lesions, endothelioma, or multiple myeloma. Closer study reveals a differentiation.

Of all the skeletal manifestations of hypothyroidism perhaps the one most often unrecognized is stippled epiphyses of hypothyroidism. The characteristic pathologic changes of deficiency in centers of ossification, with irregularity of bone growth in addition to other characteristic changes at the epiphyseal plate, serve to differentiate this condition from Legg-Calvé-Perthes disease.

The osteoporotic changes of hyperthyroidism due to negative calcium balance are of great importance. Spontaneous fractures or fractures with little exciting cause have been reported in decalcified bones of a long-standing hyperthyroidism.

With thorough knowledge and understanding of the bone lesions described, treatment may be attempted on a more rational basis. Needling of so-called aneurysms of the spine will be attempted less often when one realizes that these lesions are often due to a thyroid metastasis. Thyroid substitution therapy in cases of stippled epiphyses is a great aid when definite evidence of hypothyroidism is established. Osteoporosis due to hyperthyroidism is sometimes benefited by thyroidectomy.

## REFERENCES

1. Aub, J. C., Bauer, W., Heath, C., and Roper, M.: Studies of Calcium and Phosphorous Metabolism: Effects of Thyroid Hormone and Thyroid Disease, *J. Clin. Investigation* 7: 97-137, 1929.
2. Bartels, E. C., and Haggart, G. E.: Osteoporosis in Hyperthyroidism, *New England J. Med.* 219: 373, 1938.
3. Benjamin, Bernard, and Miller, Philip: Hypothyroidism as a Cause of Disease of the Hip, *Am. J. Dis. Child.* 55: 1189, 1938.
4. Bodenheimer, M., and Bareham, I. S.: Pulsating Tumor Due to Thyroid Metastasis, *Bull. Hosp. Joint Dis.* 2: 20-27, 1941.
5. Cruickshank, M. M.: Thyroid Metastasis in Bone, *Indian M. Gaz.* 73: 656, 1938.
6. Dinsmore, Robert S., and Kieken, N. Fred: Metastasis From Malignant Tumors of the Thyroid; a Study of 124 Cases, *Am. J. Surg.* 24: 202, 1934.
7. Dunlop, H. F., and Moore, A. B.: Osteoporosis, Secondary to Hyperthyroidism, *M. Clin. North America* 12: 1511-1519, 1929.
8. Erhardt, Oscar: Die Anatomie und Klinik der Struma maligna, *Beitr. z. klin. Chir.* 35: 343, 1902.
9. Hunter, D.: Calcium and Phosphorous Metabolism, *Lancet* 1: 947-957, 1930.
10. Kaplan, Ira: Benign Metastatic Bone Involvement From Thyroid Tumors, *Am. J. Surg.* 23: 559, 1934.

with four volumes of absolute alcohol and the resulting precipitate was taken up in minimum amounts of either. Cerebroside impurities were removed by chilling and centrifugation. The ether solution was reprecipitated with four volumes of absolute alcohol and the precipitate filtered, washed with alcohol and acetone, and desiccated. The stock solution was prepared by dissolving 100 mg. of sheep brain cephalin and 300 mg. of cholesterol in 8 c.c. of ether. The testing emulsion was prepared by adding 1 c.c. stock ether solution to 35 c.c. freshly distilled water, warmed to 65° C. and then heated slowly to boiling. The mixture was allowed to simmer until the final volume was reduced to 30 c.c., a process which disperses all coarse granular clumps and removes all traces of ether. The emulsion was then cooled to room temperature and 1 c.c. of the emulsion added to 0.2 c.c. of the patient's serum diluted with 4 c.c. of physiologic saline solution. The test tubes were allowed to stand at room temperature and were observed at the end of twenty-four and forty-eight hours as to the amount of flocculation and precipitation that had taken place.

A four-plus flocculation is indicated by complete precipitation, leaving the supernatant liquid water clear. Gradations of reaction between four-plus and negative may be found. As a general rule the reaction occurred within a few hours, with sera showing three-plus or four-plus flocculations, whereas one-plus and two-plus reactions might be observed at the end of twenty-four to forty-eight hours. No specimen was regarded as negative until forty-eight hours had elapsed without flocculation. The importance of avoiding such contaminants as anticoagulants, heavy metals, and strong acids has been emphasized by Hanger.<sup>1</sup>

In our first trials with the cephalin flocculation test we desired to control our method of preparation by testing with normal sera which should have shown negative reactions. However, we soon found that varying degrees of flocculation could be obtained, even four-plus reactions, in a most unpredictable manner. Communication with Dr. Hanger resulted in our receiving a preparation of cephalin which he had used in his observations. This preparation was darker in color and more gummy than those we had used, and gave reactions with normal sera which were entirely negative. The differences in flocculation are apparently dependant upon differences in "aging" and oxidation of the cephalin. Accordingly, in all subsequent observations we used Dr. Hanger's preparation and a preparation obtained from the Difco Company,\* which we assayed and found to have approximately the same sensitivity. It was immediately apparent, however, that preparations of cephalin might vary in sensitivity depending upon slight variations in the preparation procedure and the "age" of the preparation. Rosenberg<sup>5</sup> has recently observed differences in the reaction obtained with

\*We wish to thank Dr. C. W. Christensen of the Difco Laboratories of Detroit, Mich., for a generous supply of cephalin.

# THE CEPHALIN-CHOLESTEROL FLOCCULATION TEST IN THE JAUNDICED PATIENT

SAMUEL B. NADLER, PH.D., M.D., AND M. F. BUTLER, M.S.,  
NEW ORLEANS, LA.

*(From the Joseph Hume Research Laboratory, Touro Infirmary, the Department of Medicine, Tulane University School of Medicine, and the Ochsner Clinic)*

THE importance of a determination which might differentiate between obstructive jaundice and jaundice caused by destructive processes in the liver has been emphasized by Hanger:<sup>1</sup> "Patients with grave hepatitis are often subjected to the added hazard of an anesthetic and laparotomy to rule out possible biliary tract obstruction, while conversely, operation may be delayed perilously long in cases of obstruction in the hope that the jaundice will subside spontaneously." The differentiation clinically between these two types of jaundice is "frequently impossible despite careful history taking and physical examination, and the employment of many types of diagnostic procedure."

Hanger has recently demonstrated<sup>1, 2, 4</sup> that emulsions of sheep brain cephalin and cholesterol are regularly flocculated by sera of jaundiced patients with hepatocellular damage. Since such flocculation was not obtained with sera of normal individuals and patients with uncomplicated obstruction of the biliary tract, this simple test should prove of importance in the differential diagnosis of jaundice. Pohle and Stewart<sup>3</sup> attempted to evaluate the cephalin flocculation test in the light of various liver function tests, and were unable to confirm all of Hanger's findings. Most significantly, they found that nearly 80 per cent of cases of obstructive jaundice gave positive flocculation tests. Their data indicate that the cephalin flocculation test is of little or no value in the differential diagnosis of the two types of jaundice. Certain facts concerning the cephalin flocculation test, however, are agreed upon; viz., that (1) the test is negative in normal individuals, (2) it is only rarely if ever positive in patients without hepatic disease, (3) it is a more sensitive indicator of active liver parenchymatous disturbance than any of the so-called liver function tests, and (4) it provides the best available indicator as to prognosis in hepatic disease, especially in cirrhosis.<sup>4</sup> The purpose of this paper is to report our findings in jaundiced patients for the sole intent of evaluating the cephalin flocculation determination as a method of differentiating hepatocellular and obstructive jaundice.

## METHODS AND MATERIALS

Sheep brain cephalin was obtained by dehydration of sheep brain with three extractions of acetone and three extractions with peroxide-free ether. The concentrated ether extracts were then precipitated

with four volumes of absolute alcohol and the resulting precipitate was taken up in minimum amounts of ether. Cerebroside impurities were removed by chilling and centrifugation. The ether solution was reprecipitated with four volumes of absolute alcohol and the precipitate filtered, washed with alcohol and acetone, and desiccated. The stock solution was prepared by dissolving 100 mg. of sheep brain cephalin and 300 mg. of cholesterol in 8 c.c. of ether. The testing emulsion was prepared by adding 1 c.c. stock ether solution to 35 c.c. freshly distilled water, warmed to 65° C. and then heated slowly to boiling. The mixture was allowed to simmer until the final volume was reduced to 30 c.c., a process which disperses all coarse granular clumps and removes all traces of ether. The emulsion was then cooled to room temperature and 1 c.c. of the emulsion added to 0.2 c.c. of the patient's serum diluted with 4 c.c. of physiologic saline solution. The test tubes were allowed to stand at room temperature and were observed at the end of twenty-four and forty-eight hours as to the amount of flocculation and precipitation that had taken place.

A four-plus flocculation is indicated by complete precipitation, leaving the supernatant liquid water clear. Gradations of reaction between four-plus and negative may be found. As a general rule the reaction occurred within a few hours, with sera showing three-plus or four-plus flocculations, whereas one-plus and two-plus reactions might be observed at the end of twenty-four to forty-eight hours. No specimen was regarded as negative until forty-eight hours had elapsed without flocculation. The importance of avoiding such contaminants as anticoagulants, heavy metals, and strong acids has been emphasized by Hanger.<sup>1</sup>

In our first trials with the cephalin flocculation test we desired to control our method of preparation by testing with normal sera which should have shown negative reactions. However, we soon found that varying degrees of flocculation could be obtained, even four-plus reactions, in a most unpredictable manner. Communication with Dr. Hanger resulted in our receiving a preparation of cephalin which he had used in his observations. This preparation was darker in color and more gummy than those we had used, and gave reactions with normal sera which were entirely negative. The differences in flocculation are apparently dependant upon differences in "aging" and oxidation of the cephalin. Accordingly, in all subsequent observations we used Dr. Hanger's preparation and a preparation obtained from the Difco Company,\* which we assayed and found to have approximately the same sensitivity. It was immediately apparent, however, that preparations of cephalin might vary in sensitivity depending upon slight variations in the preparation procedure and the "age" of the preparation. Rosenberg<sup>5</sup> has recently observed differences in the reaction obtained with

\*We wish to thank Dr. C. W. Christensen of the Difco Laboratories of Detroit, Mich., for a generous supply of cephalin.

TABLE I  
CASES OF JAUNDICE CAUSED BY OBSTRUCTION OF EXTRAHEPATIC BILIARY DUCTS

CASE NO.	INITIALS	SEX	AGE	DIAGNOSIS	BASIS FOR DIAGNOSIS	FLOCCULATION	ICTERUS INDEX	REMARKS
1	L.M.	M	73	Common duct stone	Operative	0	80	Test 1 plus when repeated
2	E.B.	F	30	Common duct stone	Clinical	+	60	Reaction 2 plus after operation
3	M.T.	F	83	Common duct stone	Autopsy	0	100	
4	M.H.	F	64	Common duct stone	Operative	0	75	Died after craniotomy
5	H.L.	F	50	Common duct stone	Operative	+	50	Negative flocculation 2 days later
6	M.P.	F	50	Common duct stone	Operative	+	60	Septicemia; died eighth postoperative day
7	C.N.R.	F	64	Common duct stone	Operative	0	45	Adenocarcinoma of ovary; metastasis to gall bladder
8	A.H.	F	61	Stricture of common bile duct	Operative	0	120	Associated cholecystitis
9	L.D.	F	40	Stricture of common bile duct	Operative	+	70	Died ninth postoperative day
10	B.P.	M	3 mo.	Congenital obliteration of bile ducts	Autopsy	+	60	Bile peritonitis
11	E.P.	M	58	Carcinoma of stomach	Operative	0	115	Complicating bronchopneumonia
12	B.R.	F	53	Carcinoma of pancreas	Clinical	0	100	Metastasis to liver and bile duct
13	B.D.	M	56	Carcinoma of pancreas	Operative	0	170	Patient left before operation
14	W.C.	M	76	Carcinoma of pancreas	Clinical	0	100	Obstruction common bile duct
15	V.D.	F	54	Carcinoma of pancreas	Operative	0	30	Obstruction common bile duct
16	J.H.	M	54	Carcinoma of pancreas	Operative	0	200	Obstruction common bile duct
17	S.W.	M	34	Carcinoma of pancreas	Clinical	0	35	Obstruction common bile duct
18	R.T.	M	60	Carcinoma of pancreas	Operative	+	100	Deserted
19	T.G.	M	41	Carcinoma of ampulla of Vater	Operative	+	125	
20	S.C.	M	60	Carcinoma of pancreas	Autopsy	+	50	
21	G.J.	F	29	Cholelithiasis	Operative	0	80	Syphilis; chronic cholecystitis
22	M.H.	F	46	Cholelithiasis	Clinical	0	60	Syphilis; chronic cholecystitis
23	M.M.	F	23	Cholelithiasis	Operative	0	100	Chronic cholecystitis
24	A.T.	M	48	Cholelithiasis	Clinical	0	12	
25	A.L.	M	57	Cholelithiasis	Operative	0	30	Chronic cholecystitis
26	J.H.	F	36	Cholelithiasis	Operative	0	50	Chronic cholecystitis
27	L.N.	F	49	Cholelithiasis	Clinical	0	50	X-ray diagnosis
28	P.F.	M	65	Cholelithiasis	Operative	0	50	

various cephalin preparations and suggested that cephalin be exposed to the air for a number of weeks to convert it to the "oxidized" form in order that false positive reactions may be avoided. Emulsions were freshly prepared on the day the tests were to be performed and a "normal" serum, to check suspension stability, was used as a control. The sera were obtained from jaundiced patients in Touro Infirmary and New Orleans Charity Hospital.\* The sera of 50 jaundiced patients were studied.

The cases are divided into (1) cases of jaundice caused by obstruction of the extrahepatic biliary tract, and (2) cases of jaundice with hepatitis, but without demonstrable obstruction of the extrahepatic biliary tract.

1. *Cases of Jaundice Caused by Obstruction of Extrahepatic Biliary Tract.*—This group of 28 cases included practically all of the common types of obstructive processes involving the extrahepatic biliary tract; viz., stone in common bile duct, acute cholecystitis and cholelithiasis, stenosis of the common bile duct, congenital obliteration of the bile ducts, metastatic carcinoma of the liver and biliary tract, carcinoma of the head of the pancreas. From Table I, it is apparent that of the 28 cases, 20 showed negative flocculations, 7 gave a one-plus reaction, and 1 gave a two-plus reaction. The latter was complicated by septicemia. The 7 faintly positive reactions may have been caused by a low-grade hepatocellular damage associated with obstruction. Significantly no reaction stronger than a two-plus reaction was obtained. Two cases of obstructive jaundice showing three-plus reactions were omitted from Table II. One of these was diagnosed clinically as obstructive jaundice. The icteric index was 35 and the flocculation three-plus. One week later the flocculation was negative. The patient was operated upon the following day and cholecystgastrostomy performed. The head of the pancreas was indurated and the regional nodes enlarged. No malignancy was demonstrated. The final diagnosis was hepatitis and pancreatitis. It is doubtful that this case was one of extrahepatic obstruction. The second case had carcinoma of the head of the pancreas with a tremendously enlarged liver which extended 13 cm. below the costal margin. No liver sections were available. This case was obviously one of marked hepatitis complicating the picture of obstruction. On the basis of the above data, it seems reasonable to conclude that in obstructive jaundice the cephalin flocculation is predominantly negative or faintly positive.

2. *Cases of Jaundice With Hepatitis, But Without Demonstrable Obstruction of Extrahepatic Duct.*—These cases may be subdivided into two groups: (a) cases with acute catarrhal jaundice of unknown etiology, and undiagnosed hepatitis, and (b) cases caused by some chemical toxin. The first group comprises 12 cases with icteric indices

\*We are indebted to Dr. William McCord of New Orleans Charity Hospital for collecting a number of sera from jaundiced patients.



TABLE II  
CASES OF JAUNDICE WITH HEPATITIS BUT WITHOUT DEMONSTRABLE OBSTRUCTION OF EXTRAHEPATIC DUCT

CASE NO.	INITIALS	SEX	AGE	DIAGNOSIS	BASIS FOR DIAGNOSIS	FLOCCULATON	ICTERUS INDEX	REMARKS
1	G.R.	F	21	Acute catarrhal jaundice	Clinical	+++	100	Recovery
2	J.S.	M	5	Acute catarrhal jaundice	Clinical	+++	50	Recovery
3	M.S.	F	30	Acute catarrhal jaundice	Clinical	+++	150	Recovery
4	J.S.	M	49	Acute catarrhal jaundice	Clinical	+++	150	Recovery
5	I.D.	F	41	Acute catarrhal jaundice	Clinical	+++	75	Recovery
6	W.W.	M	50	Acute catarrhal jaundice	Clinical	+++	150	Recovery
7	A.C.	M	10	Acute catarrhal jaundice	Clinical	+++	85	Recovery
8	J.C.	M	40	Acute catarrhal jaundice	Clinical	+++	100	Recovery
9	G.K.	M	58	Acute catarrhal jaundice	Clinical	+++	120	Recovery
10	C.J.	F	19	Acute catarrhal jaundice	Clinical	+++	85	Recovery
11	E.H.	M	58	Acute hepatitis	Clinical	+++	200	Recovery
12	A.D.	M	50	Acute hepatitis	Clinical	+++	400	Complications: bronchopneumonia, Type I pneumococcal bacteremia; died
13	J.B.	F	51	Acute alcoholism	Clinical	+	30	Recovery
14	T.G.	F	33	Toxic hepatitis	Clinical	++	70	Lysol burns of mouth, stomach, etc.
15	L.H.	F	25	Sulfathiazole hepatitis	Clinical	0	50	Pyelitis of pregnancy
16	V.W.	M	18	Arsphenamine hepatitis	Clinical	+++	32	Five-day mapharsen drip
17	D.J.	M	46	Arsphenamine hepatitis	Clinical	0	65	Recovery
18	L.H.	M	25	Arsphenamine hepatitis	Clinical	0	90	Recovery
19	B.G.	F	35	Arsphenamine hepatitis	Clinical	0	80	Recovery
20	L.H.	F	17	Arsphenamine hepatitis	Clinical	0	125	Recovery

as high as 400. In this group, three- and four-plus reactions were the rule. All patients except the one in Case 12 made an uneventful clinical recovery. Case 12 had a Type 1 pneumococcal bacteremia, bronchial pneumonia, syphilis, and a possible amoebic hepatitis.

The second group comprises cases of jaundice associated with some obvious poison including alcohol, sulfathiazole, and arsphenamine. In our small series the reactions obtained with these drugs are not predictable and are not particularly cogent from the diagnostic standpoint, for the etiologic factor responsible for the jaundice is apparent. Our results with arsphenamine are similar to those obtained by Hanger.<sup>1</sup> Recently Hanger and Patek<sup>4</sup> have published an extensive series of cases of cirrhosis of the liver in which the reaction may vary from a four-plus to a negative, depending upon the clinical status of the patient. The diagnostic and prognostic significance of their findings has been discussed by them. In cases with three- and four-plus reactions the speed with which the positive flocculation reaction appeared in the test tube was noticeably shorter than time reactions for one- and two-plus flocculation reactions.

#### DISCUSSION

In this series of cases of jaundice, our findings tend to confirm the observations of Hanger. Cases of jaundice caused by obstruction in the extrahepatic ducts give either negative or faintly positive reactions with the cephalin flocculation test. Rosenberg<sup>5</sup> has recently obtained similar results in 11 cases of obstructive jaundice proved by operation. Cases of jaundice associated with acute hepatitis give strongly positive reactions. In addition, we have noted that cases of jaundice associated with some obvious chemical poison may give unpredictable reactions. The data indicate clearly that there is a definite diagnostic significance to the cephalin flocculation test in the differential diagnosis of these two types of jaundice. Diametrically opposite conclusions were reached by Pohle and Stewart.<sup>3</sup>

While the duration and completeness of obstruction may be predominating factors in determining the amount of associated hepatitis, the data on the patients observed by Pohle and Stewart, Hanger, and ourselves are too different to be reconciled on the basis of differences in the degree of associated hepatitis. A more likely explanation would seem to be that Pohle and Stewart used a preparation which was more sensitive than the ones used by Hanger and ourselves. Indeed, Hanger has suggested that this may be the case.<sup>4</sup> We incline toward a similar view, even though Pohle and Stewart used a preparation less sensitive than our original preparations, in that they demonstrated negative flocculation reactions with normal sera. It would seem important that a single source supply of emulsion material should be used if accumulated data are to have comparative value. The cephalin-cholesterol material supplied to us by Difco Company seems trustworthy and is

being assayed in our laboratory at the present time. There seems to be some indication that it will soon be available on the market.

#### SUMMARY

The cephalin flocculation test was done on sera obtained from 50 jaundiced patients. A definite difference in flocculation reaction was observed in cases of jaundice caused by obstruction of the extrahepatic biliary tract and in cases of jaundice with hepatitis, but without demonstrable obstruction of the extrahepatic duct. On the basis of our data it seems justifiable to conclude that the cephalin flocculation reaction is of diagnostic value in the differential diagnosis of obstructive jaundice and jaundice caused by hepatitis. The importance of the use of a uniform preparation, obtained from a single large standardized batch, in a larger series of cases has been emphasized. It is recommended that the test be applied to the sera of all jaundiced patients.

#### REFERENCES

1. Hanger, F. M.: Serological Differentiation of Obstructive From Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, *J. Clin. Investigation* 18: 261, 1939.
2. Hanger, F. M.: The Flocculation of Cephalin-Cholesterol Emulsions by Pathological Sera, *Tr. A. Am. Physicians* 53: 148, 1938.
3. Pohle, F. J., and Stewart, J. K.: The Cephalin-Cholesterol Flocculation Test as an Aid in the Diagnosis of Hepatic Disorders, *J. Clin. Investigation* 20: 241, 1941.
4. Hanger, F. M., and Patek, A. J.: The Cephalin Flocculation Test in Cirrhosis of the Liver, *Am. J. M. Sc.* 202: 48, 1941.
5. Rosenberg, D. H.: The Cephalin-Cholesterol Flocculation Test in Cases of Disease of the Liver, *Arch. Surg.* 43: 231, 1941.

# AN EVALUATION OF INTESTINAL SUCTION IN INTESTINAL OBSTRUCTION

JAMES B. BLODGETT, M.D., BOSTON, MASS.

*(From the Laboratory for Surgical Research, Harvard Medical School, and the Surgical Service of the Peter Bent Brigham Hospital)*

INTESTINAL suction was introduced for the treatment of intestinal obstruction almost four years ago.<sup>1</sup> Enough data are now available so that statistical evaluation of this therapy is possible.

## SELECTION OF CASES

The cases used in this analysis are derived from a study of all cases of intestinal obstruction treated at the Peter Bent Brigham Hospital from 1933 to July, 1941. To these have been added all available cases from the American literature that satisfy the requirements of the classification.

When the influence of any one factor on a series of cases is to be studied, the test series should be as similar as possible to the control series except in respect to the factor under consideration. The control series in this study is therefore comprised of cases treated since Wangenstein<sup>2, 3</sup> established duodenal suction as an accepted therapy in obstruction. Prior to this it had been recognized that control of the fluid and electrolyte balance was essential in the treatment of intestinal obstruction. The test series consists only of cases in which the Miller-Abbott tube, or other long tube, had definitely passed into the jejunum.

In order to compare similar types of intestinal obstruction, two distinct groups were chosen for analysis: (1) simple mechanical obstruction of the small or large bowel; (2) intestinal obstruction associated with peritonitis. It will be seen that the mortality of these two groups is so different that they must be considered separately in evaluating any therapy applied to them.

"Paralytic ileus" not associated with peritonitis is too poorly defined a clinical entity to constitute a definite group for an analysis of this sort, although individual cases may yield satisfactorily to intestinal suction.

## STATISTICAL METHOD

Obviously, no statistical significance can be attached to the difference in percentages of two series unless the difference is considerably greater than that which might occur through chance. The range of the probable variation of the difference between percentages in two

being assayed in our laboratory at the present time. There seems to be some indication that it will soon be available on the market.

#### SUMMARY

The cephalin flocculation test was done on sera obtained from 50 jaundiced patients. A definite difference in flocculation reaction was observed in cases of jaundice caused by obstruction of the extrahepatic biliary tract and in cases of jaundice with hepatitis, but without demonstrable obstruction of the extrahepatic duct. On the basis of our data it seems justifiable to conclude that the cephalin flocculation reaction is of diagnostic value in the differential diagnosis of obstructive jaundice and jaundice caused by hepatitis. The importance of the use of a uniform preparation, obtained from a single large standardized batch, in a larger series of cases has been emphasized. It is recommended that the test be applied to the sera of all jaundiced patients.

#### REFERENCES

1. Hanger, F. M.: Serological Differentiation of Obstructive From Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, *J. Clin. Investigation* 18: 261, 1939.
2. Hanger, F. M.: The Flocculation of Cephalin-Cholesterol Emulsions by Pathological Sera, *Tr. A. Am. Physicians* 53: 148, 1938.
3. Pohle, F. J., and Stewart, J. K.: The Cephalin-Cholesterol Flocculation Test as an Aid in the Diagnosis of Hepatic Disorders, *J. Clin. Investigation* 20: 241, 1941.
4. Hanger, F. M., and Patek, A. J.: The Cephalin Flocculation Test in Cirrhosis of the Liver, *Am. J. M. Sc.* 202: 48, 1941.
5. Rosenberg, D. H.: The Cephalin-Cholesterol Flocculation Test in Cases of Disease of the Liver, *Arch. Surg.* 43: 231, 1941.

difference (3.1), the reduction in the mortality due to the use of intestinal suction is of undeniable significance because the odds are 369 to 1 against this difference being the result of chance.

TABLE II  
MECHANICAL INTESTINAL OBSTRUCTION (INTESTINAL SUCTION USED)

AUTHORS	CASES	DEATHS
Abbott <sup>10</sup>	14	2
Wise <sup>11</sup>	3	0
Wangenstein et al. <sup>7</sup>	9	3
Leigh et al. <sup>12</sup>	38	1
Duncan <sup>13</sup>	3	0
Willson <sup>14</sup>	22	0
Bennett <sup>15</sup>	9	0
Glenn <sup>9</sup>	34	5
Peter Bent Brigham Hospital	19	1*
	151	12 (7.9% mortality)

\*This was a 42-year-old female who was given fair relief of symptoms of obstruction by intestinal suction but who died of multiple carcinomatosis.

#### INTESTINAL OBSTRUCTION COMPLICATED BY PERITONITIS

When peritonitis is associated with intestinal obstruction, the mortality is greatly increased. To evaluate the effect of intestinal suction on this condition, our cases have been added to all acceptable cases appearing in the literature. No distinction was made on the basis of the extent of peritoneal involvement. The cases treated without intestinal suction are listed in Table III and those treated with intestinal

TABLE III  
OBSTRUCTION WITH PERITONITIS (INTESTINAL SUCTION NOT USED)

AUTHORS	CASES	DEATHS
Van Buren and Smith <sup>5</sup>	13	12
Leigh et al. <sup>12</sup>	7	6
Peter Bent Brigham Hospital	36	23*
	56	41 (73.1% mortality)

\*Causes of death: 17 patients failed to be improved by gastric or duodenal suction; 12 suffered from pulmonary complications which contributed to their death (7, atelectasis; 5, pneumonia).

The age distribution was 3 cases under 30 years; 11 cases, 30 to 59 years; the remainder, over 60 years.

suction appear in Table IV. The total number of cases in each group is not large, because authors seldom list their cases of obstruction and peritonitis separately and satisfactory intubation is difficult in the presence of peritonitis. However, the difference in mortality percentages of these groups is highly significant. The mortality in the control series of cases with obstruction and peritonitis that were not treated with intestinal suction is 73.1 per cent. But the mortality in the same type of case when treated with intestinal suction is 25 per cent. The difference between 73.1 and 25 per cent is 48, which is more than five times the standard error of the difference (8.2) and thus of undeniable statistical significance. The odds are greater than a million to one that the difference is not due to chance.

series can be computed by a formula\* and is known as the standard error of the difference.<sup>4</sup> The formula takes into account the total number of cases in each series and also the individual percentages to be compared. To be statistically significant, the difference between the percentages of two compared series must be at least 2.5 times the computed standard error of the difference. This fact may become clearer if stated in another manner. The probability that the difference between percentages of any two series is due to chance may be determined mathematically by comparing the difference with the computed standard error of the difference. If the difference between the percentages is 2.5 times their standard error, the odds are 80 to 1 that the difference did not occur by chance; if the difference is 3 times their standard error, the odds are at least 369 to 1 against the difference being due to chance.

#### SIMPLE MECHANICAL INTESTINAL OBSTRUCTION

Fifty-six cases of mechanical intestinal obstruction were treated without intestinal suction at the Peter Bent Brigham Hospital between 1933 and 1941. Table I summarizes the mortality figures of these cases and

TABLE I

MECHANICAL INTESTINAL OBSTRUCTION (INTESTINAL SUCTION NOT USED)

AUTHORS	CASES	DEATHS
Van Buren and Smith <sup>5</sup>	78	15
Scudder et al. <sup>6</sup>	14	3
Wangensteen et al. <sup>7</sup>	116	13
Glenn <sup>9</sup>	42	14
Peter Bent Brigham Hospital	56	8*
	306	53 (17.3% mortality)

\*Five cases failed to improve with gastric or duodenal suction. Seven cases had obstruction due to malignancy. All but 2 patients, who were essentially moribund, had complications contributing to their death: 2 patients died of circulatory failure (1 due to heart failure, the other due to shock); 2 cases were complicated by pneumonia and 2 by pulmonary emboli.

of the cases of mechanical intestinal obstruction appearing in the American literature between the time that duodenal suction was generally used and intestinal suction was introduced. This is a control series of 306 cases with a mortality of 17.3 per cent.

Table II gives the cases and deaths in mechanical intestinal obstruction treated with intestinal suction. The total number of cases is 151; the mortality is 7.9 per cent or essentially 8 per cent.

It appears, therefore, that when intestinal suction is added to the usual measures of treatment of mechanical intestinal obstruction, the mortality is reduced from 17.3 to 8 per cent. Since the difference between these percentages (9.3) is three times the standard error of the

$$\cdot \sqrt{\frac{\text{Percentage A} \times (100 - \text{Percentage A})}{\text{No. of Cases in Series A}}} \text{ plus } \frac{\text{Percentage B} \times (100 - \text{Percentage B})}{\text{No. of Cases in Series B}}$$

## DISCUSSION

This evidence that the use of intestinal suction is an essential factor in reducing the mortality of intestinal obstruction parallels the experience of Johnston<sup>18</sup> and Leigh and his co-workers<sup>12</sup> in their own clinics.

TABLE VII

ANALYSIS OF PETER BENT BRIGHAM HOSPITAL CASES OF INTESTINAL OBSTRUCTION WITH PERITONITIS (INTESTINAL SUCTION NOT USED)

ETIOLOGY OF PERITONITIS AND OBSTRUCTION	NO. OF CASES	OPERATION		DIED
		YES	NO	
Appendicitis	10	10		3
Perforations of gastrointestinal tract	7	5		2
			2	2
Inflammation of female internal genitals	3	3		1
Ulcerative colitis	1	1		1
Septic abortion	1	1		1
Prostatectomy postoperatively	1	1		1
Carcinoma of large bowel	10	9		8
			1	1
Lymphosarcoma of small bowel	2	2		2
Metastatic carcinoma of small bowel	1	1		1

TABLE VIII

ANALYSIS OF PETER BENT BRIGHAM HOSPITAL CASES OF MECHANICAL OBSTRUCTION WITH PERITONITIS (INTESTINAL SUCTION USED)

ETIOLOGY	NO. OF CASES	OPERATION		DEATHS
		YES	NO	
Appendicitis	3	3		2
Perforation of large bowel	2	2		0
Inflammation of female internal genitals	1	1		0
Total hysterectomy postoperatively	1	1		0

Intestinal suction is an ideal physiologic treatment because it produces an outlet for the intestinal contents at a point just proximal to the obstruction. As the intestine is decompressed, the circulation is improved, the smooth muscle regains its normal tone, and the important function of nutrition may be resumed. When the pressure within the intestine is released, the volume of circulating plasma, which has been shown to be reduced in obstruction, is restored to normal. Reduction of the intra-abdominal pressure by the decompression of the intestine allows normal circulation in the great venous channels and normal diaphragmatic excursion. Preoperative decompression of the alimentary tract by intestinal suction may avoid the necessity of colostomy or enterostomy and presents the operator with undistended bowel of normal thickness and tone. Intestinal suction continued into the postoperative period protects the anastomosis by preventing intraluminal pressure which might "blowout" the suture line or impair its circulation.



TABLE IV  
OBSTRUCTION WITH PERITONITIS (INTESTINAL SUCTION USED)

AUTHORS	CASES	DEATHS
Abbott <sup>10</sup>	3	1
Leigh et al. <sup>12</sup>	14	1
Penberthy et al. <sup>16</sup>	6	2
Duncan <sup>13</sup>	1	0
Bennett <sup>15</sup>	4	4
Glenn <sup>9</sup>	14	2
Wangensteen et al. <sup>7</sup>	3	1
Peter Bent Brigham Hospital	7	2*
	52	13 (25% mortality)

\*One patient was a 58-year-old female with generalized peritonitis due to acute appendicitis with perforation. Duodenal suction for eight days gave little improvement. Intestinal suction for seven days reduced x-ray evidence of distention but did not improve patient's condition. She died of overwhelming peritonitis of *Bacillus coli* and *Streptococcus faecalis* origin. The other patient was a 69-year-old male with generalized peritonitis due to acute appendicitis with perforation. Intestinal suction for eight days prevented x-ray evidence of distention. Patient died of peritonitis and toxic hepatitis.

TABLE V  
ANALYSIS OF PETER BENT BRIGHAM HOSPITAL CASES OF MECHANICAL OBSTRUCTION  
(INTESTINAL SUCTION NOT USED) (1933-JULY, 1941)

ETIOLOGY OF OBSTRUCTION	NO. OF CASES	SITE OF OBSTRUCTION		OPERATION		DEATHS
		SMALL BOWEL	LARGE BOWEL	YES	NO	
Postoperative adhesions				24		1
	28	28			4	0
Gallstone	2	2		2		0
Impacted fecalith	1	1		1		0
		2		2		0
Carcinoma	25		23	22		6
					1	1

TABLE VI  
ANALYSIS OF PETER BENT BRIGHAM HOSPITAL CASES OF MECHANICAL OBSTRUCTION  
(INTESTINAL SUCTION USED)

ETIOLOGY OF OBSTRUCTION	NO. OF CASES	SITE OF OBSTRUCTION		OPERATION		DEATHS
		SMALL BOWEL	LARGE BOWEL	YES	NO	
Postoperative adhesions				5		0
	11	11			6	0
	1	1			1	0
Femoral hernia				1		0
	7	2			1	1
Carcinoma			5	5		0

The mortality in 306 cases of mechanical obstruction treated without intestinal suction is 17.3 per cent. In 151 cases of the same type treated with intestinal suction the mortality is 7.9 per cent.

The mortality in 56 cases of obstruction with associated peritonitis treated without intestinal suction is 73 per cent. But in 52 cases of the same condition treated with intestinal suction the mortality is 25 per cent.

The clinical value of intestinal suction in reducing the mortality of obstruction justifies the effort of acquiring and applying the technique.

# REFERENCES

1. Abbott, W. O., and Johnston, C. G.: Intubation Studies of the Human Small Intestine, Surg., Gynec. & Obst. 66: 691-697, 1938.
2. Wangensteen, O. H.: Therapeutic Considerations in Management of Acute Intestinal Obstruction: Technique of Enterostomy and Further Account of Decompression by Employment of Suction-Siphonage by Nasal Catheter, Arch. Surg. 26: 933-961, 1933.
3. Wangensteen, O. H., and Paine, J. R.: Treatment of Acute Intestinal Obstruction by Suction With the Duodenal Tube, J. A. M. A. 101: 1532-1539, 1933.
4. Campbell, H. E.: The Statistical Method, SURGERY 9: 825-831, 1941.
5. Van Buren, F. T., and Smith, B. C.: Acute Ileus, Ann. Surg. 107: 321-329, 1938.
6. Scudder, John, Zwemer, R. L., and Whipple, A. O.: Acute Intestinal Obstruction—Evaluation of Results in 2,150 Cases With Detailed Studies of 25 Showing Potassium as a Toxic Factor, Ann. Surg. 107: 161-197, 1938.
7. Wangensteen, H. O., Rea, C. W., Smith, B. A., Jr., and Schwyzer, H. C.: Experiences With the Employment of Suction in Treatment of Acute Intestinal Obstruction, Surg., Gynec. & Obst. 68: 851-868, 1939.
8. Miller, T. G., and Abbott, W. O.: Intestinal Intubation—A Practical Technique, Am. J. M. Sc. 187: 595-599, 1934.
9. Glenn, P. M.: Intestinal Obstruction—Results of Treatment With Use of Intestinal Intubation, Am. J. Digest. Dis. 8: 35-39, 1941.
10. Abbott, W. O.: Intubation of Small Intestine: Treatment of Intestinal Obstruction and Procedure for Identifying Lesion, Arch. Int. Med. 63: 453-468, 1939.
11. Wise, Robert A.: The Miller-Abbott Double Lumen Tube in Intestinal Obstruction—A Preliminary Report, Am. J. Surg. 41: 412-418, 1938.
12. Leigh, Octa C., Nelson, J. A., and Swenson, P. C.: The Miller-Abbott Tube as an Adjunct to Surgery of Small Intestinal Obstructions, Ann. Surg. 111: 186-212, 1940.
13. Duncan, John A.: Miller-Abbott Intestinal Intubation. Evaluation in Treatment of Intestinal Obstruction, Northwest Med. 39: 177-179, 1940.
14. Willson, D. M.: Intestinal Intubation: Experiences in the Medical Management of Patients With Obstructing Lesions of the Small and Large Intestine, Proc. Staff Meet. Mayo Clin. 15: 372-377, 1940.
15. Bennett, L. C.: Intubation Management of Distension in Intestinal Obstruction, West. J. Surg. 49: 71-76, 1941.
16. Penberthy, G. C., Noor, R. J., and Benson, C. D.: The Treatment of Adynamic Ileus by Gastro-Intestinal Intubation in Children, Surg., Gynec. & Obst. 71: 211-217, 1940.
17. Fine, J., Hurwitz, A., and Mark, J.: A Clinical Study of Plasma Volume in Acute Intestinal Obstruction, Tr. Am. S. A. 58: 64-74, 1940.
18. Johnston, C. G.: Decompression in Treatment of Intestinal Obstruction, Surg., Gynec. & Obst. 70: 365-369, 1940.
19. Whipple, A. O.: The Use of the Miller-Abbott Tube in the Surgery of the Large Bowel, SURGERY 8: 289-298, 1940.
20. Blodgett, J. B.: A Technique for the Satisfactory Use of the Miller-Abbott Tube, Am. J. Surg. 53: 271-279, 1941.

Lest this evidence be considered as indicating the desirability of intestinal suction in all cases of obstruction, the contraindications should be emphasized. When a reasonable possibility of vascular strangulation exists, intestinal suction should not be resorted to except as preparation for immediate operation. The danger is that although decompression offers no relief for the vascular obstruction, it may mask the symptoms to such an extent as to minimize the urgency of operation which is the essential therapy for intestinal strangulation. The decision for immediate operation depends upon wise clinical judgment of all facts at hand. If strangulation cannot be ruled out, surgery should be advised. Willson<sup>14</sup> and others have pointed out that intestinal intubation should not be attempted in cases of obstruction of the large bowel which show great distention of the colon and little evidence of distention of the small bowel. The rationale of this suggestion is that under these circumstances, the ileocecal valve is still competent and does not permit the pressure within the large bowel to be relieved by regurgitation into the ileum. In such cases, the dangerous pressure on the colon cannot be reduced until the tip of the long tube has passed through the ileocecal valve. The passage of the tube through the whole small bowel may not be complete for days, and even then it may be impossible to get the tip to pass through the competent ileocecal valve. Accordingly, intestinal intubation is not the treatment of choice because the relief of pressure in the large bowel may be unwisely delayed.

The reduced mortality from the proper use of intestinal suction depends upon successful intestinal intubation and the maintenance of continuous suction. Intubation may be difficult or, rarely, impossible. During intubation and suction, both patient and apparatus require the closest supervision and attention to details. It is the universal experience of clinics using the technique extensively that the number of failures of intestinal suction is greatly reduced by increased knowledge of the details of technique and earlier decisions to employ intestinal suction.<sup>18</sup> Whipple<sup>19</sup> states: "The reason that so many hospitals have failed to appreciate the value of the Miller-Abbott tube in dealing with cases of ileus is that no one person has learned the application and technique of the method and acquired the experience necessary to its success." The details of the technique of the method have been published by those who devised the apparatus and others who have had clinical experience in its use.<sup>10, 12, 17, 20</sup> Whatever effort is involved in acquiring and applying the technique is certainly justified by the fact that intestinal suction is a life-saving procedure as an adjunct to the treatment of obstruction.

#### CONCLUSIONS

The use of intestinal suction in the treatment of intestinal obstruction has resulted in a statistically significant reduction in mortality.

manometer (specific gravity, 1.5), and intestinal motility was recorded on the kymograph. The fistulas had been installed for carcinoma of the intestine, ileitis, or colitis. At the time of the experiments the patients were in good condition. A control period of at least thirty minutes was taken to establish the prevailing rhythm of intestinal motility. After that each patient received an intramuscular injection of 1 mg. of prostigmine methylsulfate, and during another test performed one to two weeks later, 1 mg. of prostigmine\* plus 50 gammas of acetylcholine. The record was continued for two to four hours following the injection.

In the animal experiments, normal dogs anesthetized with nembutal were employed. Blood pressure was recorded from the carotid artery and heparin was used as antieoagulant. Intestinal motility was recorded by balloons inserted in the jejunum, the ileum and the colon, using the same type of manometer as described above. All injections were given intravenously.

#### RESULTS

Fifteen human subjects with intestinal fistulas were used. The records of all fifteen patients used regularly showed stimulation of intestinal motility by prostigmine and prostigmine-acetylcholine. No difference was found, however, between the prostigmine and acetylcholine-prostigmine mixture. This may have been due to the small amount of acetylcholine employed. In previous experiments on animals with peritonitis, we have found that the combination of eserine and acetylcholine produced more intestinal motility than eserine alone.<sup>2</sup> We believe that in our present experiments, the acetylcholine was not destroyed by the blood esterase because it must have been adequately protected against this enzyme by the rather large amount of prostigmine injected with it. We did not wish, however, to take the risk of injecting larger amounts of acetylcholine in view of untoward reactions which we had experienced in previous work. In a number of patients intestinal motility was stimulated so strongly by prostigmine that the balloon was pushed out of the fistula and in some cases evacuation of fecal material occurred. A few patients experienced cramps which were not particularly strong or disturbing.

Meyer and Neeches<sup>5</sup> have reported tests on patients with megaesophagus in whom the injection of prostigmine was followed by increased tone and peristalsis of the esophagus, and in experiments on esophageal motility of the dog they have been able to show that prostigmine was still effective on the esophagus after atropinization of the animal; that is, that prostigmine had an effect not only through the parasympathetic nerves, but also directly on the musculature. The experiments on the dog reported here were therefore conducted with

\*Supplied by Hoffmann-La Roche, Inc., Nutley, N. J.

# A STUDY ON THE MECHANISM OF ACTION OF PROSTIGMINE ON INTESTINAL MOTILITY IN THE HUMAN BEING AND IN THE DOG\*

ARTHUR H. SCHWARTZ, M.S., M.D., IRVING REINGOLD, M.D., AND  
H. NECHELES, M.D., PH.D., CHICAGO, ILL.†

(From the Departments of Gastro-Intestinal Research and Surgery,  
Michael Reese Hospital)

ESERINE has been used by veterinarians to overcome distention and atony of the intestinal canal in animals. In recent years eserine has been employed for the same conditions in the human being and in two reports from this laboratory its effects on intestinal motility of normal dogs and of dogs with peritonitis have been demonstrated.<sup>1, 2</sup> Recently prostigmine, an eserine derivative, has been used widely due to its relative lack of the undesirable by-effects of eserine.

While many reports have been published on the effects of eserine<sup>1, 2</sup> and of prostigmine<sup>3 et al.</sup> on intestinal motility in the normal and in the diseased man and animal, we have been interested in another angle of this question; namely, whether under pathologic conditions such as peritonitis, inflammation or distention of the intestine, any or enough acetylcholine would be liberated at the parasympathetic nerve endings of the intestine to produce peristalsis. It has been shown recently that nervous impulses failed to be transmitted to the effector organs when vascular tone was low.<sup>4</sup> The effects of eserine or prostigmine in the usual doses administered to man are considered to be due to their inhibitory action on blood esterase, the ferment which hydrolyses acetylcholine after it has been formed at the nerve endings and has acted on the intestinal musculature. If under pathologic conditions, normal activity of the parasympathetics should be abolished, and if the effects of eserine or prostigmine would be only through stimulation of parasympathetic activity, we could not expect beneficial effects under these conditions. With these questions in mind tests were performed on patients with ileostomies, cecostomies, or colostomies, and on normal anesthetized dogs.

## METHODS

The patients had taken nothing by mouth since the night preceding the test, which was performed in the morning. A rubber balloon was inserted into the fistula and connected to an oil carbon tetrachloride

\*Aided by the Gustav M. Rothchild Fund.

†We are obliged to Dr. Alfred Strauss and Dr. Siegfried Strauss for the use of their patients.

Received for publication, Sept. 10, 1911.

too small, and that with a larger dose distinct effects would have been obtained, but we did not want to use higher doses in view of the dangers involved in such a combination of drugs, and in view of the relative weakness of our subjects. The experiments on the dog have given us valuable experience concerning the mechanism of prostigmine on the intestine, and we feel certain that this experience can be applied to the human being as well; namely, that the motor effect of prostigmine on the intestine is not only an indirect one through the endings of the parasympathetic nerves, but also a direct one on the musculature of the intestinal canal. Acetylcholine alone had no effect following a large dose of atropine. This was not the case when prostigmine was given; that is, its direct muscular effect had become evident. Prostigmine, therefore, produces intestinal motility not only by an indirect effect through the parasympathetic nerves, but also by a direct effect on the intestinal musculature, as we were able to show also for the esophagus.<sup>5</sup> We conclude, therefore, that when the parasympathetic nerves or their endings in the intestine have suffered following pathologic conditions, prostigmine may yet be expected to be effective due to its direct muscular effects, provided that the intestinal musculature is still viable. It is evident, however, that prostigmine or any similar drug should not be given in case of damaged intestine which may be expected to perforate.

#### SUMMARY AND CONCLUSIONS

The effect of intramuscular injection of 1 mg. of prostigmine to patients with ileal, cecal, or colonic fistulas has been tested. In every instance a good response of intestinal motility lasting from thirty to sixty minutes was found. A mixture of prostigmine and acetylcholine did not have any better effect than prostigmine alone. No serious or disturbing by-effects of the injection of prostigmine were observed. In experiments on dogs it was found that the effects of prostigmine on the intestinal musculature are twofold; namely, through stimulation of the parasympathetics and through direct stimulation of the intestinal musculature. Following atropinization of the animal, acetylcholine was not effective, while prostigmine still evoked distinct rhythmic motility and increased tone of jejunum and colon. We feel, therefore, that the administration of prostigmine to patients with intestinal paralysis, in whom the nervous motor mechanism may have suffered, is a good procedure. The weight of the patient should be considered in the computation of the dose of prostigmine. Patients below 125 pounds of body weight should receive proportionately less than 1 mg., which seems to be adequate for persons at or above that weight. In cases of impending perforation of the intestinal walls prostigmine should not be used.

this experience in view. If the intestine reacted to prostigmine after atropinization, this purely muscular effect of prostigmine would give us the assurance that in a damaged intestine in which the parasympathetic stimuli could not be effective, we might still be able to produce motility with its beneficial effects such as evacuation of gas, fecal material, etc.

Fig. 1 represents a typical experiment on a dog. Following a suitable control period, the injection of 0.5 mg. of prostigmine intravenously was followed by a steep rise of tonus of the colon and defecation. Tonus and motility of the jejunum rose likewise, but not as markedly as that of the colon. Following this, 2 mg. of atropine was injected intravenously and was followed by a decrease of tone and of contractions of both jejunum and colon. Twenty-five minutes later, the intravenous injection of 0.5 mg. of prostigmine was followed by increase of tone and motility of the jejunum and slightly increased motility of the colon. When the same injection was repeated nine minutes later, both colon and jejunum responded with increased tone and motility. Twenty-eight minutes later, an additional dose of 2 mg. of atropine was injected intravenously in an attempt to obtain more complete atropinization. Nevertheless, 1 mg. of prostigmine still evoked motility and tone in jejunum and colon. After atropinization, the blood pressure depressing effect of prostigmine was abolished. A dose of 50 gammas of acetylcholine injected intravenously did not affect jejunal and colonic motility following the last injection of prostigmine.

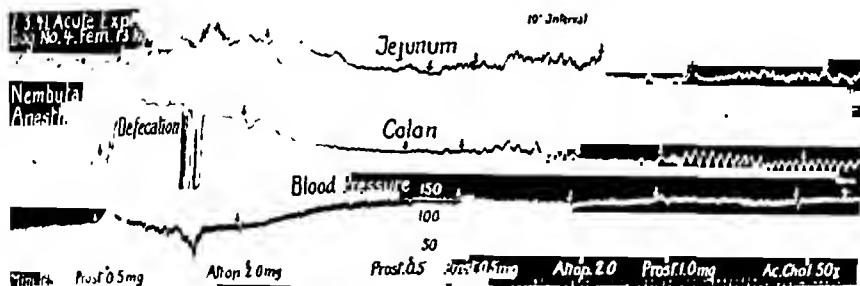


Fig. 1.—Intravenous injections: (1) prostigmine methylsulfate, 0.5 mg.; (2) atropine sulfate, 2.0 mg.; (3 and 4) prostigmine methylsulfate, 0.5 mg.; (5) atropine sulfate, 2.0 mg.; (6) prostigmine methylsulfate, 1.0 mg.; (7) acetylcholine HCl, 50 gammas.

#### DISCUSSION

In the experiments on the patients, we have found that a dose of 1 mg. of prostigmine was safe and without any serious or disagreeable by-effects, except slight cramps in a few patients, and that a combination of 1 mg. of prostigmine with 50 gammas of acetylcholine was not more effective in producing intestinal motility than 1 mg. of prostigmine by itself. We feel that the dose of acetylcholine may have been

too small, and that with a larger dose distinct effects would have been obtained, but we did not want to use higher doses in view of the dangers involved in such a combination of drugs, and in view of the relative weakness of our subjects. The experiments on the dog have given us valuable experience concerning the mechanism of prostigmine on the intestine, and we feel certain that this experience can be applied to the human being as well; namely, that the motor effect of prostigmine on the intestine is not only an indirect one through the endings of the parasympathetic nerves, but also a direct one on the musculature of the intestinal canal. Acetylcholine alone had no effect following a large dose of atropine. This was not the case when prostigmine was given; that is, its direct muscular effect had become evident. Prostigmine, therefore, produces intestinal motility not only by an indirect effect through the parasympathetic nerves, but also by a direct effect on the intestinal musculature, as we were able to show also for the esophagus.<sup>5</sup> We conclude, therefore, that when the parasympathetic nerves or their endings in the intestine have suffered following pathologic conditions, prostigmine may yet be expected to be effective due to its direct muscular effects, provided that the intestinal musculature is still viable. It is evident, however, that prostigmine or any similar drug should not be given in case of damaged intestine which may be expected to perforate.

#### SUMMARY AND CONCLUSIONS

The effect of intramuscular injection of 1 mg. of prostigmine to patients with ileal, cecal, or colonic fistulas has been tested. In every instance a good response of intestinal motility lasting from thirty to sixty minutes was found. A mixture of prostigmine and acetylcholine did not have any better effect than prostigmine alone. No serious or disturbing by-effects of the injection of prostigmine were observed. In experiments on dogs it was found that the effects of prostigmine on the intestinal musculature are twofold; namely, through stimulation of the parasympathetics and through direct stimulation of the intestinal musculature. Following atropinization of the animal, acetylcholine was not effective, while prostigmine still evoked distinct rhythmic motility and increased tone of jejunum and colon. We feel, therefore, that the administration of prostigmine to patients with intestinal paralysis, in whom the nervous motor mechanism may have suffered, is a good procedure. The weight of the patient should be considered in the computation of the dose of prostigmine. Patients below 125 pounds of body weight should receive proportionately less than 1 mg., which seems to be adequate for persons at or above that weight. In cases of impending perforation of the intestinal walls prostigmine should not be used.



## REFERENCES

1. Frank, R., Zimmerman, L., and Necheles, H.: Effect of Eserine and Acetylcholine on Gastro-Intestinal Motility in Normal Dogs, *Proc. Soc. Exper. Biol. & Med.* 32: 686, 1935.
2. Zimmerman, L., Frank, R., and Necheles, H.: Effect of Acetylcholine and of Physostigmine on Gastro-Intestinal Motility. Observations of Normal Animals and of Animals With Experimental Peritonitis, *Arch. Surg.* 33: 187, 1936.
3. Harger, J. R., and Wilkey, J. L.: Management of Postoperative Distension and Ileus, *J. A. M. A.* 110: 1165, 1938.
4. Buelbring, E., and Burn, J. H.: Vascular Changes Affecting the Transmission of Nervous Impulses, *J. Physiol.* 97: 250, 1939.
5. Meyer, Jacob, and Necheles, H.: Cardiospasm. Observations on the Use of Prostigmine—A Clinical and Experimental Report, *J. Lab. & Clin. Med.* 27: 162, 1941.

# EXPERIMENTAL INVESTIGATION OF GASTROINTESTINAL SECRETIONS AND MOTILITY FOLLOWING BURNS AND THEIR RELATION TO ULCER\*

H. NECHELES, M.D., PH.D., AND WM. H. OLSON, CHICAGO, ILL.

(From the Department of Gastro-Intestinal Research, Michael Reese Hospital)

ALTHOUGH gastrointestinal ulcers following burns are not frequent, there is no doubt that their incidence has been higher than that of a normal population.<sup>1</sup> Many theories concerning the cause of Curling's ulcer have evolved during the last 100 years, but no systematic work on gastrointestinal secretions and motility following burns was found. Harkins reviewed the literature extensively in 1938 and found it to be rather contradictory.<sup>1</sup> A number of authors have held toxic substances to be responsible for the development of Curling's ulcer. These substances have been believed to be the product of the burn in the affected area and have been supposed to damage the gastric and duodenal mucosa either directly from the blood, or indirectly from the bile following their excretion in the liver, or still more indirectly by diminution of bile secretion through the toxic effects of such substances on the liver. Gastric hyperacidity following burns, acting on areas already damaged by burn toxins, were held responsible by Levin in 1929,<sup>2</sup> but Wilson in 1935<sup>3</sup> could not confirm this. Levin's assumption of hyperacidity<sup>2</sup> was not based on any experimental or factual evidence. Tinel and Ungar reported increased volume of gastric secretion following immersion of the foot of an anesthetized dog in water of 50° C. for two minutes.<sup>4</sup>

Our work was directed to observations on the effects of burns on gastrointestinal secretions and motility.

The literature on the effects of shock in general on the gastrointestinal mucosa of man has been reviewed recently by Harkins,<sup>1</sup> Penner and Bernheim,<sup>5-7</sup> and Klemperer and collaborators.<sup>8</sup> From a study of the literature and from our own experience we know that following shock from any kind of trauma, gastritis, duodenitis, or enteritis with petechiae, congestion, edema of the mucous membranes, and erosions or ulcers may be found.

*Experimental Technique and Procedure.*—Normal, healthy, fasting dogs (thirty hours) were anesthetized with pentobarbital sodium (nembutal) or with ether, and were kept under anesthesia for the entire duration of the experiment. Unless the animals died, they were destroyed rapidly and, needless to say, painlessly at the termination of the experiments. Blood pressure was recorded in the usual way from

\*Aided by the A. B. Kuppenheimer Fund. A preliminary report was read at the Meeting of the Am. Physiol. Soc., Chicago, 1941.  
Received for publication, Oct. 14, 1941.

the carotid artery with a mercury manometer. Respiration was recorded by a cuff placed round the chest; intra-abdominal pressure from a balloon placed between liver and diaphragm; and gastric, duodenal, and colonic motility by balloons placed in these organs. The various motilities were recorded by manometers filled with a mixture of oil and carbon tetrachloride, with a specific gravity of 1.5. Gastric secretion was collected either by suction from a tube tied in the pylorus, or by gravity from a cannula in the most dependent part of the stomach, the animal being placed on its abdomen on an operating table tilted upward at an angle of about 30°; in other experiments the esophagus was ligated in the neck and the pylorus just beyond the sphincter, and gastric secretions were collected at the termination of the experiment. Salivary secretion was collected from one submaxillary duct, biliary secretion from the common duct, with the cystic duct ligated, and pancreatic secretion from the main pancreatic duct. Each drop of these secretions was recorded by an instrument described by us.<sup>9</sup> The volume of gastric juice was marked on the kymograph record for every 10 c.c. of secretion collected. In one group of animals the unstimulated fasting secretions were collected. In another group secretions were stimulated at regular intervals during the control period and following trauma or burns.

More or less extensive torch burns were applied to the hindleg and the lower part of the back. In one experiment one hindleg was scalded.

A number of animals were used as controls to determine the effects of anesthesia alone. In order to check the degree of shock in the controls and in the shock series, circulating time,<sup>11</sup> plasma CO<sub>2</sub>, hematocrit, hemoglobin and plasma proteins were determined in most experiments.

## RESULTS

### A. Secretions.—

1. *Controls for Salivary, Pancreatic, and Biliary Secretion.*—In 4 control experiments without burns constant injection of glucose (5 per cent)-saline (0.9 per cent) solution at the rate of 2 c.c. per minute was administered by a pump described previously.<sup>10</sup> Hourly intravenous injections of pilocarpine nitrate, 0.25 to 0.5 mg., or of secretin,\* 5 to 10 mg., were given alternately, and in the following a change of secretion denotes changes in stimulated secretions.

In 3 of the control animals, in which salivary secretion was recorded, no change was noted. Two of these experiments lasted twelve hours and 1 lasted six hours. Of 3 control experiments, in which bile secretion was recorded, in 1 no change was noticed over a period of twelve hours and in the other 2 a slight decrease occurred in experiments lasting twelve and four hours respectively. In 3 experiments, in which pancreatic secretion was recorded, no change was noted in experiments lasting twelve, twelve, and four hours respectively. In all control animals

\*Kindly supplied by Dr. D. Klein, of the Wilson Laboratories, Chicago, Ill.

blood pressure fell gradually as the experiments progressed, but the animals maintained a mean blood pressure of about 100 mm. during the greater part of the experiment.

## 2. Burns.—

(a) *Salivary, Pancreatic, and Biliary Secretion*: Control periods of several hours' duration preceded the burn. All animals received constant infusion of glucose-saline solution and alternating injections of pilocarpine and secretin, as described above, under "Controls." Experiment 1 lasted six and one-half hours; blood pressure fell gradually from 115 to 40; salivary secretion decreased 50 per cent. Biliary secretion was not affected by the first small burn on one leg, but decreased by 50 per cent following more extensive burns. Pancreatic secretion was diminished 50 per cent. The volume of gastric secretion rose considerably following the burn (Table I, Experiment 26). Dog 2, in an experiment lasting ten hours, showed salivary and gastric secretions (Table I, Experiment 27) considerably increased following a burn, while biliary secretion decreased 50 per cent. After a second and third more extensive burn, biliary secretion was inhibited 75 per cent and urinary secretion 50 per cent (collected from one cannulated ureter). In Dog 3, in which one hindleg was scalded, blood pressure gradually dropped from 150 to 40, and a 60 per cent decrease of salivary, biliary, and pancreatic secretions was noted. Gastric secretion rose considerably (Table I, Experiment 28). The experiment lasted six hours.

(b) *Gastric Secretion (Tables I and II)*: In Experiments 4, 5, 13, and 23 to 29 esophagus and pylorus were ligated and gastric juice was collected from a cannula (v.s.). In the other experiments esophagus and pylorus were ligated and gastric contents measured at the termination of the experiment. A solution of 0.9 per cent NaCl with 5 per cent glucose was used when constant injection was given.

Tables I and II show that the resting stomach of 10 anesthetized animals secreted small amounts of fluid varying between 0 and 10 c.c. per hour (controls of Experiments 3 to 5, 11 to 13, and 17). Intravenous infusions of saline-glucose solution, starving\* for thirty hours, feeding† ten hours before the experiments, and the injection of pilocarpine (Experiments 26 to 29) did not affect this secretion noticeably; its acidity was low, with no free acid and between 10 and 20 degrees of combined acid (i.e., cubic centimeters of N/10 HCl in 100 c.c. of gastric juice).

When animals were subjected to burns, those not receiving intravenous infusions did not show a significant change in gastric secretion. On the other hand, in the experiments in which intravenous infusion was administered, the quantity of gastric secretion rose considerably in volume in all animals, and in acidity in a number of them. Administration of food ten hours before the burn seemed to enhance the secretion of acid. In the experiments in which drugs were employed (Experiments 23

\*All animals had access to water.

†Meat, cereals, bread, and vegetables.

GASTRIC SECRETION FOLLOWING BURNS

TABLE I

INTRAVENOUS			GASTRIC SECRETION				GASTROINTESTINAL PATHOLOGY (AND REMARKS)		
EXPERIMENT NO.	INFUSION	INJECTIONS DRUGS	CONTROL		AFTER BURN				
	C.C. PER MIN.		HR.	C.C. PER HR.	TIME PERIOD	VOLUME C.C.		C.C. PER HR.	
Starving; no infusion; burn									
1						6 hr.	22	3.7	Slight duodenitis
2						6 hr.	80	13.3	
Starving; infusion; no burn								None	
3	17		1½	2.7					Gastritis and edema
Starving; infusion; burn									
4	5		3½	2.9	First burn	30 min.	11	22.0	
					120 min.		2	1.0	
					45 min.		10	12.5	
					35 min.		10	17.0	
					40 min.		5	7.5	
					Second burn	75 min.	10	8.0	
5	3		3	10.0	45 min.		10	13.3	
					9 hr.		33	30.0	Gastritis and prepyloric ulcer (acidity 74/85)
6	5					4 hr.	20	5.0	Edema
7	5					4 hr.	175 (acid)	44.0	Edema (acidity 120/126)
8	17					4 hr.	75	19.0	Edema
9	6					6 hr.	48	8.0	Food in stomach; edema, duodenitis, ileitis
10	5					6 hr.	42 (acid)	7.0	Edema, slight gastritis fundus, severe enteritis (acidity 12/43)
Fed; no infusion; no burn									
11			6	2.5					Slight duodenitis
12			6	3.3					
Fed; no infusion; burn									
13			2	0.5		4 hr.	2.5	0.6	None
14						5 min.	15-20		None

15					4 hr.	15	4.0	None
16					4 hr.	20	5.0	Stomach contracted and edematous
Fed; infusion; no burn								
17	6		7					Stomach mucosa very dry, anterior and posterior walls sticking together
Fed; infusion; burn								
18	7				5¾ hr.	215 (acid)	37.4	Duodenal mucosa edematous and hemorrhagic; pancreas normal (acidity 97/106)
19	5				5¼ hr.	108 (acid)	20.6	Slight duodenitis (acidity 54/91)
20	6				5½ hr.	108 (acid)	19.6	Edema of gastric mucosa (acidity 36/50)
21	6				7 hr.	145 (acid)	20.7	Slight gastritis and duodenitis (acidity 15/29)
22	4				7½ hr.	175	23.3	Food in stomach; edema of gastric mucosa; severe duodenitis and ileitis
Starved; infusion; drugs; burn (except Experiment 23, no burn)								
23*	4†	Histamine	6					None
24*	4†	Histamine			6 hr.	120	20.0	Gastritis, ulcers, edema
25	4†	Histamine	2		4 hr.	24	6.0	Gastritis and edema
26	3	0.5 mg. pilocarpine nitrate intravenously every hour	3½		6 min.	28	280.0	
					7 min.	2	17.0	
					27 min.	10	22.0	
					45 min.	10	13.3	
					95 min.	30	19.0	
27	3	As above	3½		1 min.	25	(1500)	
					30 min.	30	60.0	
28	4	As above	2		45 min.	17	23.0	
29	6	0.5 mg. pilocarpine nitrate intravenously every half hour			2 hr.	25	12.5	Gastritis and edema

\*Litter mates, same breed, sex, weight.

†5 mg. %.

‡8 mg. % histamine HCl in saline (0.9%)—glucose (5%) solution. Anesthesia with nembutal, except with ether in experiment 6.

TABLE II  
SUMMARY OF GASTRIC SECRETIONS FOLLOWING BURNS

TOTAL NO. OF EXPERIMENTS	PROCEDURE	AVERAGE SECRETION PER HOUR C.C.	NO. OF EXPERIMENTS WITH FREE ACID
10	No burns, all experiments*	3.0	0
3	No infusion	2.1	0
7	Infusion	3.4	0
4	Burns, fed or starved, no infusion†	3.3	0
7	Starved, infusion	17.4	3 out of 7
5	Fed, infusion‡	24.1	4 out of 5

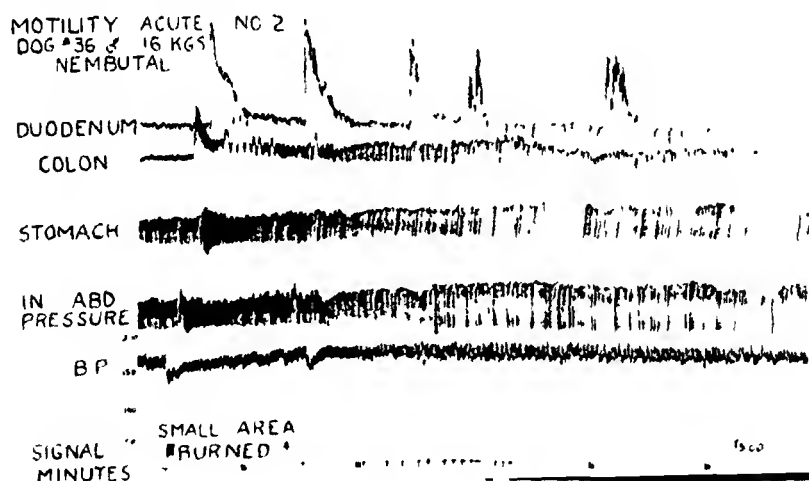
\*Except histamine Experiments (No. 23-25).

†Except Experiments 2 (dog sick) and 14 (died 5 minutes after burn).

‡Except histamine and pilocarpine experiments (No. 23-29).

to 29) similar results were obtained, except in Experiment 25 in which secretion decreased after a burn, although histamine had been given by constant injection.

In the experiments in which pilocarpine was administered (Experiments 26 to 29), surprisingly low volumes of secretion were obtained during the control periods; following burns the volumes rose to a considerable degree, but not acidity.



A.

Figs. 1 A and B.—Gastrointestinal motility and intra-abdominal pressure following burns. Note increase of intra-abdominal pressure following third burn.

The increase in the rate of volume secretion seemed to be greatest immediately following the burn, sometimes during the first few minutes (see Experiments 4, 26, and 27).

The amount of secretion seemed to be related to the appearance of free acid so far as the presence of free acid accompanied the larger volumes of secretion, but the reverse was not always true. Food in the

stomach may abolish free acidity (Experiment 22). In Experiment 5 only 33 c.c. of an alkaline fluid was discharged from the cannula in the pylorus, but when the stomach was opened it was found to contain 233

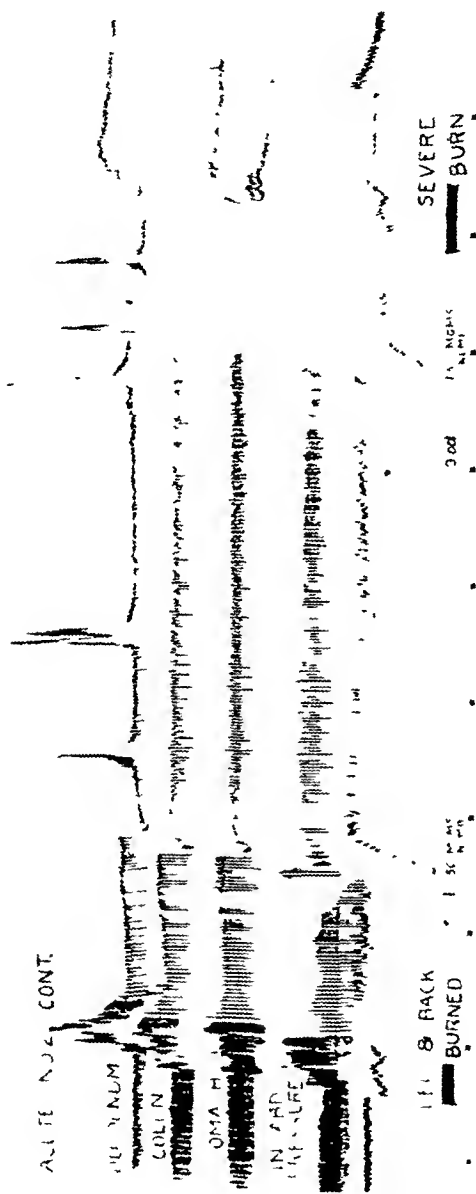


FIG. 1B.

c.c. of secretion with 74 and 85 degrees of free and total acidity. In this dog the presence may be assumed, of a spasm of the musculus sphincter antri, which separated the antrum and the body of the stomach. This assumption is supported by our observations on the



motility of the stomach after burns and by the findings in a case of a burned child. The dog in the above-mentioned Experiment 5 had a prepyloric ulcer and a marked degree of gastritis.

### *B. Motility.—*

In the experiments reported above a great increase in the rate and depth of respiration and a strong contraction of the abdominal wall were noted to follow a burn in animals in a deep state of anesthesia, with absence of the corneal reflex. In the following experiments respiration, intra-abdominal pressure, and gastrointestinal motility were investigated following burns.

In 2 experiments motility of duodenum, colon, and stomach was recorded, together with intra-abdominal pressure and blood pressure. In Experiment 1 a notable increase in intra-abdominal pressure and respiration followed the burn, with little effect on gastrointestinal motility per se, except that produced by intra-abdominal pressure and respiration. The blood pressure in this dog fell very little. In the second experiment (Fig. 1) considerable duodenal motility with strong and prolonged contractions followed the first and second burns. Following a third more severe burn of the legs and the lower part of the back a marked increase in intra-abdominal pressure and an increase in colonic motility were noted. As will be shown below, gastric motility following a burn is strongest in the pyloric antrum, and a stomach balloon will indicate little of this activity.

In order further to analyze gastric motility following burns, 13 experiments were performed, using various procedures. In 2 experiments the abdomen was kept open and the stomach exposed to direct observation. The viscera were kept moist throughout the experiments. In 3 experiments the chest was opened, the phrenic nerves cut, and artificial respiration was administered. In most experiments a balloon was introduced into the pyloric antrum through the pylorus, and in some experiments another balloon was inserted into the body of the stomach through the esophagus. In a number of animals the vagi were cut in the neck and the splanchnic nerves above the diaphragm. A number of animals received 1 to 4 mg. of atropine sulfate intravenously before or following a burn. Blood pressure and respiration or intra-abdominal pressure were recorded. Hemoglobin, hematocrit, plasma  $\text{CO}_2$ , plasma proteins, and circulating time were determined in most of the experiments.

Fig. 2 demonstrates a typical experiment. During a control period of twenty minutes little antrum motility was apparent. Following the first burn, antrum motility and tone were greatly augmented. Section of both vagi did not abolish antrum motility, but modified it, due apparently to the change in respiration. Following a second burn, an even greater degree of gastric motility occurred; section of the vagi seemed to enhance the motor effects of burns on the pyloric antrum.

The intravenous injection of 2 mg. of atropine sulfate abolished antrum motility completely for about 100 minutes. A slight degree of motility reappeared later, but a third burn failed to evoke the usual motility which was observed in control experiments to follow three or four subsequent burns. Two similar experiments were performed, with identical results.

Section of both vagi and splanchnics did not abolish antrum motility following a burn, and a subsequent burn elicited strong increase in antrum tone and motility.

In 4 experiments simultaneous balloon records from the pyloric antrum and from the body of the stomach were obtained. Motility of the corpus of the stomach was apparent following burns, but it was of lesser degree than that of the antrum. Both were abolished by intravenous injection of 2 to 4 mg. of atropine sulfate, and subsequent burns failed to elicit them.

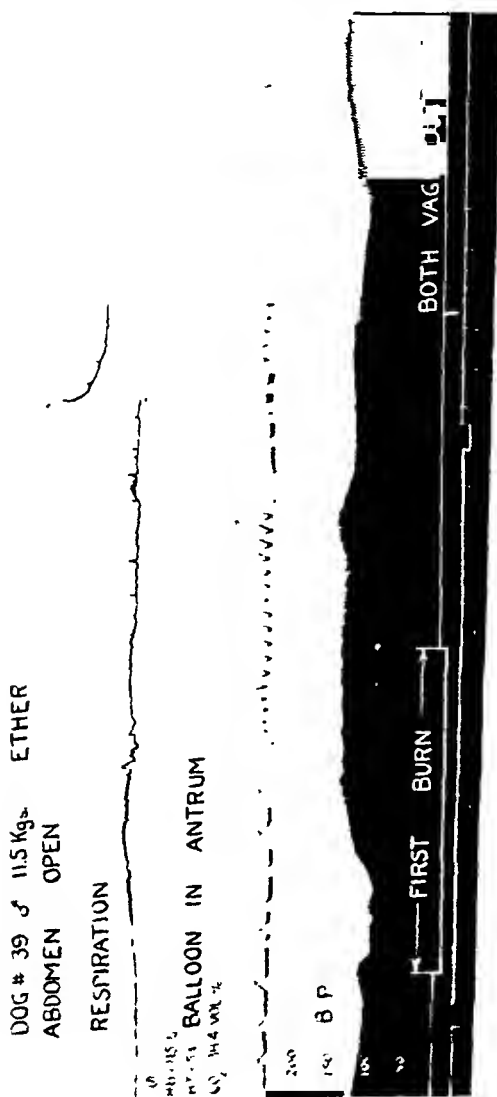
The duration of gastric motility following a burn varied between twenty minutes and two hours. Antrum motility persisted for longer periods of time than motility of the corpus of the stomach.

The experiments in which the stomach had been exposed for observation amplified the above experiences. In one such experiment no gastric motility was seen during a period of twenty-five minutes before the burn. Immediately after the start of the burning, the antrum began to show contractions, followed shortly by the corpus. The entire stomach contracted tonically to about one-half its size. The contractions of the antrum began at the height of the incisura angularis and were regular and forceful, with a rate of one or two per minute, giving the impression of pulsations. The waves of contraction stopped at the pylorus and none were observed to pass into the duodenum. The duodenum contracted tonically. Section of the vagi did not affect gastric motility, but injection of 2 mg. of atropine sulfate abolished motility and relaxed the stomach completely within five minutes. Another burn, applied twenty minutes later, did not evoke gastric motility or increase in tone.

In another similar experiment the first burn produced strong motility of antrum and stomach. A second burn, following section of the vagi, was followed by such forceful antrum motility that the distal part of the antrum was forced over the pyloric canal, giving the impression of an intussusception. Two milligrams of atropine intravenously abolished tone and contractions for ninety-four minutes, after which a third burn caused small increase of tone and shallow ripples of motility mainly of the antrum. Following the first burn, the gall bladder contracted to about one-half its size, but the duodenum did not change.

The effects of atropine were uniform in all 7 experiments in which it was injected. Motility and tone of the stomach, following one or more burns, were either abolished or depressed to shallow ripples.

Intra-abdominal pressure, which was increased in every burn experiment, was not responsible for the gastric motility observed, as proved by experiments with chest opened, phrenics cut, and artificial respiration, and by direct observation. The increased intra-abdominal pressure was due to tonic contraction of the abdominal wall and of the chest, as observed directly and as shown on graphic records.



FIGS. 2 A, B, and C.—Respiration and motility of the pyloric antrum following burn. Blood pressure was well maintained throughout experiment. Note appearance of antral motility following first burn. Section of vagus did not abolish motility of first or second burn. Atropine abolished motility of second and third burn completely.

#### PATHOLOGIC FINDINGS

After burns, a considerable degree of edema of the mucosa and of gastritis and duodenitis was found in a number of animals with small erosions of the gastric and duodenal mucosa in a few animals, and a

prepyloric ulcer in one dog. Histologically this last was a typical peptic ulcer, extending to the musenlaris propria.\* The duodenitis was present also in animals in which the pylorus had been ligated, so that no gastric juice could have entered the duodenum. The edema of the mucosa of the stomach was particularly striking in those animals which had received intravenous infusion of saline-glucose solution. No macroscopic changes were found in the adrenals.

R. DOG # 39 CONT. #1

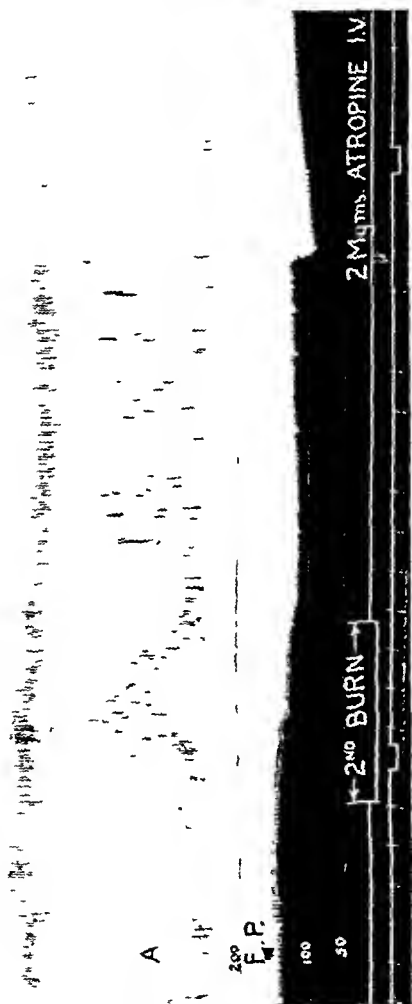


Fig. 2B.

#### CHEMICAL FINDINGS

No relationship was found between the degree of acidosis and hemoconcentration and the secretory or motor responses following burns. Most animals had blood pressures of 100 and above for the greater part of the experiment, and in nearly all of them the burns did not affect

\*We are indebted to Dr Max Appel from the Department of Pathology for advice

blood pressure greatly; in a number of dogs blood pressure rose after a burn. Urinary secretion, collected from a ureter or from the bladder in several experiments, showed a decrease of about 50 per cent, as hemoconcentration and acidosis developed. The detailed results of our studies on blood chemistry following shock from burns will appear in another paper by us.

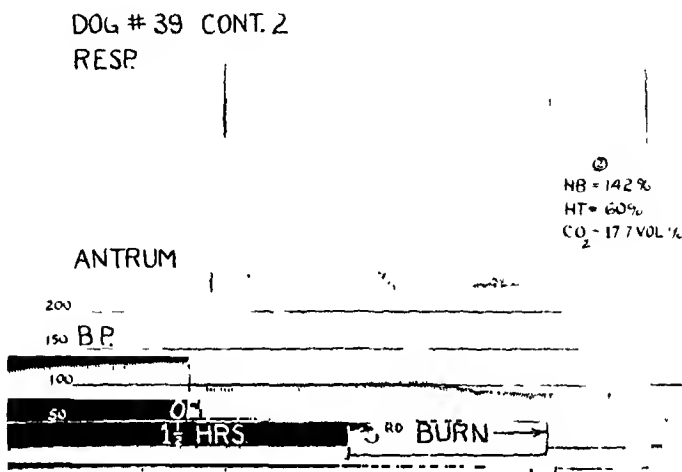


Fig. 2C.

## DISCUSSION

Following burns the volume of gastric secretion was found to be increased considerably in those experiments in which a constant intravenous infusion of saline-glucose solution was given. In the experiments without intravenous infusion no appreciable increase in volume of gastric juice was found after a burn. Feeding ten hours before the experiment seemed to result in a larger volume of secretion and a higher incidence of free acidity following a burn than resulted after starving the animal for thirty hours before the experiment. These findings may have a bearing on conditions in the human patient suffering from burns because, except during the early morning hours, the human being is in the absorptive phase of digestion, and because the human patient with burns usually receives large amounts of fluid by mouth or by elysis.

Concerning the increased volumes of secretion following burns observed in our experiments, we have to consider that the forceful contractions of the stomach may squeeze fluid out of the glandular ducts and pockets of the organ. It is hard to believe, however, that this alone can be responsible for such large volumes and continued secretion as followed the burn in a number of experiments.

Evidence is accumulating that histamine or a related compound is liberated in the skin of human beings, dogs, and other animals under the

influence of thermal trauma.<sup>12, 13, 20</sup> It may be that under conditions not known as yet, the absorption of this substance may vary,<sup>21</sup> or that deeper burns may destroy it. The rectal temperature of the dogs was not changed materially following burns. In most animals the legs and thighs were burned, in some the lower part of the back, and in one a superficial burn of the skin of the body was added. We do not believe that the intensity and duration of the burns were sufficient to raise intra-abdominal temperature and thus affect secretions.<sup>1</sup> A raised intra-abdominal temperature would tend to increase biliary secretion in anesthetized dogs.<sup>14</sup>

The increase in gastric motility following a burn cannot be attributed to histamine or like substances for the following reasons: Histamine has little or no effect on gastric motility and the response of the stomach to histamine is not abolished by relatively small doses of atropine. The prompt depressing effect of atropine on gastric motility in our burn experiments points to the presence of compounds of the nature of acetylcholine. These may be liberated by burns, or, more probably, the acetylcholine-splitting esterase may be inhibited following a burn. Acetylcholine injected either continuously or in repeated doses is able to elicit gastric secretion as well as motility,<sup>15, 16, 22</sup> and it is possible that both gastric secretion and motility may be largely stimulated by that one compound. The simultaneous decrease in stimulated salivary (except in one experiment) and pancreatic secretions and the increase in gastric secretion following burns cannot be explained at the present time. We are aware of other observations on shock or diminished blood volume which describe decreased blood flow through the submaxillary gland,<sup>17</sup> vasoconstriction of abdominal organs, varying degrees of capillary resistance in different organs,<sup>18</sup> and varying blood flow through different organs or parts of the body.<sup>19</sup> These observations are not necessarily opposed to our findings, since in our experiments a state of activity of the stomach was evident, and because biogenic compounds can act selectively on different organs. Further studies on this problem are in progress.

Our observations on decreased salivary, biliary, and pancreatic secretions following burns and observations of a considerable increase of gastric secretion and motility together with increased intra-abdominal pressure throw some light on the pathogenesis of Curling's ulcer. Although this type of ulcer becomes clinically apparent much later after the burn, it can be assumed that the local acute pathology begins to develop much earlier.

#### SUMMARY

The effects of burns on gastrointestinal secretion and motility were studied in anesthetized dogs. Salivary, biliary, and pancreatic secretions were diminished, with the exception of one experiment in

which a considerable increase in salivary secretion was observed. Gastric secretion and acidity increased in a number of experiments following a burn. In one of these animals a prepyloric ulcer was found. Increased volume of gastric secretion seemed to depend on infusions, and increased acidity seemed to be related to infusions and previous feeding of the animals.

A considerable increase in intra-abdominal pressure and of gastric motility was observed following burns; the latter was particularly strong in the pyloric antrum and began immediately after starting of the burn. Section of the splanchnic nerves and of the vagi, or of both, did not diminish or abolish gastric motility following burns. Section of the vagi seemed to enhance the gastric motor response to a burn. The intravenous injection of atropine sulfate abolished the motility of the stomach following a burn. The relation of the above findings to Curling's ulcer are discussed.

#### REFERENCES

1. Harkins, H. N.: Acute Ulcer of the Duodenum (Curling's Ulcer) as a Complication of Burns: Relation to Sepsis, *Surgery* 3: 608-611, 1935.
2. Lavin, J. J.: Duodenal Ulcer Following Burns: With the Report of Two Cases, *Brit. J. Surg.* 17: 410-413, 1929.
3. Wilson, W. C.: Extensive Burns and Scalds, *Edinburgh M. J.* 52: 177-188, 1935.
4. Tinel, J., and Ungar, G.: Vasodilatation et libération locale de substances histaminiques, *Comptes rend. Soc. de biol.* 190: 1148-1149, 1935.
5. Penner, A., and Bernheim, A. I.: Acute Postoperative Enterocolitis. A Study on the Pathologic Nature of Shock, *Arch. Path.* 27: 966-983, 1939.
6. Penner, A., and Bernheim, A. I.: Acute Postoperative Esophageal, Gastric and Duodenal Ulcerations. A Further Study of the Pathologic Changes in Shock, *Arch. Path.* 28: 129-140, 1939.
7. Penner, A., and Bernheim, A. I.: Experimental Production of Digestive Tract Ulcerations, *J. Exper. Med.* 70: 453-460, 1939.
8. Klemperer, P., Penner, A., and Bernheim, A. I.: The Gastro Intestinal Manifestations of Shock, *Am. J. Digest. Dis.* 7: 410-414, 1940.
9. Olson, Wm. H., and Neeheles, H.: Simple Modification of the Hanke Gibbs Drop Recorder, *Proc. Am. Physiol. Soc.* p. 214, 1941.
10. Neeheles, H., and Olson, Wm. H.: A Simple Constant Injection Pump, *J. Lab. & Clin. Med.* 26: 1647, 1941.
11. Olson, Wm. H., Gutmann, H., Levinson, S. O., and Neeheles, H.: Circulating Time in Shock, *War Med.* 1: 830-842, 1941.
12. Guggenheim, M.: Die Biogenen Amine, Basel, 1940, S. Karger, pp. 370-371 (Quotations 359, 360, 361, 371, 372).
13. Lambert, E. H., and Rosenthal, S. R.: A Method for the Study of Skin Histamine (With Some Results of Splanchnic Nerve Stimulation), *Proc. Am. Physiol. Soc.*, p. 170, 1941.
14. Osborne, S. L., Grodins, F. S., Goldman, L., and Ivy, A. C.: The Effect of Hyperpyrexia on the Secretion and Flow of Bile, *Am. J. Physiol.* 132: 32-41, 1941.
15. Neeheles, H., Levitsky, P., Kohn, R., Maskin, M., and Frank, R.: The Vasomotor Effect of Acetylcholine on the Stomach of the Dog, *Am. J. Physiol.* 116: 330-336, 1936.
16. Neeheles, H., Motel, W., Kosse, J., and Neuwelt, F.: The Effects of Acetylcholine, Acetylbetamethyleholine and Prostigmine on the Secretion of the Stomach of Man and Dog, *Am. J. Digest. Dis.* 5: 224-231, 1938.
17. Gesell, R.: Studies on the Submaxillary Gland. IV. A Comparison of the Effects of Hemorrhage and of Tissue-Abuse in Relation to Secondary Shock, *Am. J. Physiol.* 47: 468-506, 1919.

18. Erlanger, J., Gesell, R., and Gasser, H. S.: Studies in Secondary Traumatic Shock. I. The Circulation in Shock After Abdominal Injuries, *Am. J. Physiol.* 49: 90-116, 1919.
19. Blalock, A., and Levy, S. E.: Effect of Hemorrhage, Intestinal Trauma and Histamine on Partition of Blood Stream, *Am. J. Physiol.* 118: 734-738, 1937.
20. Kisima, H.: Ueber die Bedeutung des Histamins für Verbrennungsgifte, *Fukuoka acta med.* 31: 49-50, 1938.
21. Lam, C. R.: The Chemical Pathology of Burns, *Surg., Gynec. & Obst.* 72: 390-400, 1941.
22. Necheles, H., Neuwelt, F., Steiner, N., and Motel, W. G.: Study of a New Spasmolytic Drug: Diphenylacetyldiethylaminoethanol-Hydrochloride (Trasentin), *Am. J. Digest. Dis.* 6: 39-46, 1939.



# A NERVOUS FACTOR IN THE ETIOLOGY OF SHOCK IN BURNS

HERMAN KABAT, PH.D.,\* AND RAYMOND F. HEDIN, M.D.,  
RED WING, MINN.

*(From the Interstate Clinic and the Anderson Institute for Biological Research,  
Red Wing, Minn., and the Department of Physiology, University  
of Minnesota, Minneapolis, Minn.)*

A NUMBER of investigations have been carried out to study the significance of afferent nerve impulses in the etiology of traumatic shock. Crile<sup>1</sup> early pointed out the importance of a nervous factor in shock. O'Shaughnessy and Slome<sup>2</sup> presented convincing evidence that afferent nerve impulses from a traumatized limb play an important role in the production of shock. Lorber, Kabat, and Welte<sup>3</sup> confirmed the observation that shock occurs following trauma to an extremity disconnected from the body except for the main nerve trunks. Freedman and Kabat<sup>4</sup> showed that despite limited fluid loss, trauma results in shock, and further, that the fall in blood pressure can be prevented by preliminary transection of the lumbar spinal cord. In human abdominal surgery, Volpitto, Woodbury, and Hamilton<sup>5</sup> found evidence in arterial pulse curves for a neurogenic type of shock.

While evidence has been accumulating concerning the importance of the nervous factor in traumatic shock, no analysis of the nervous influence in burn shock has been made. Thus, Wilson,<sup>6</sup> in a recent review (1941), states: "Whether noxious nerve impulses from the injured area play any part in initiating or perpetuating secondary shock of burns is unknown." The purpose of the present investigation is to study the significance of a nervous factor in shock following burns.

## METHODS

Observations were made on 83 adult cats of both sexes, anesthetized with pentobarbital sodium administered intraperitoneally in doses of 35 mg. per kilogram. Additional barbiturate was given at intervals to maintain such a level of anesthesia that the cat was relaxed, the corneal reflex absent, but the lid closure reflex in response to touching the skin in the neighborhood of the inner canthus remained active. The anesthesia was maintained as long as the animal survived.

In one series of experiments, blood pressure was recorded from a cannula in the carotid artery by means of a mercury manometer, 5 per cent sodium citrate being used as the anticoagulant. The artery was occluded by means of a clamp except when a blood pressure reading

\*Aided by a grant from the Committee on Scientific Research of the American Medical Association.  
Received for publication, Dec. 18, 1941.

was taken two to three times per hour. In these experiments, the trachea was cannulated. In another series of experiments, no surgery was performed on the neck.

The burn, confined to the skin of one hindlimb, was produced by means of a Bunsen flame. In some experiments, the leg was burned for ten minutes, in other experiments for fifteen minutes.

The saphenous vein of the normal hindlimb was exposed and all blood samples were drawn from this vein by needle puncture. For hemoglobin determinations, 20 c.mm. of blood was drawn into a pipette, diluted with 8 c.c. of 0.1 N hydrochloric acid and the hemoglobin concentration read in a colorimeter. For determination of specific gravity of the blood, 0.0001 c.c. of heparin (Connaught, 1,000 units per c.c.) was placed in the bottom of a small test tube and evaporated to dryness by slight warming. This delayed clotting and facilitated the determination of specific gravity. Fifty cubic millimeters of venous blood was mixed with the dry heparin and specific gravity measured by means of the falling-drop apparatus,<sup>7</sup> two determinations being made on each sample of blood.

In approximately one-half of the animals, afferent impulses from the burned limb were prevented from reaching the brain by preliminary transection of the spinal cord, performed without aseptic precautions, usually thirty minutes before burning. In some animals, the spinal cord was cut at the first lumbar segment, in others at the eleventh thoracic segment. It is recognized that such cord transection has effects other than simple limb denervation, but it is believed that the latter is the most important consequence.

At the termination of the experiment, either following death or sacrifice of the animal, the thoracic and abdominal organs were examined grossly. The hind quarters were carefully separated, in the midline and weighed, the difference in limb weights being taken as a measure of the local loss of fluid in the area of the burn.

## RESULTS

*I. Blood Pressure.*—The average initial arterial pressure in 14 control cats was 120 mm. Hg. Within several minutes of initiation of thermal trauma, blood pressure had risen abruptly 40 mm. Hg (Fig. 1). During and immediately following the burn the heart rate tended to slow considerably, the pulse pressure increased, and the blood pressure tended to show sharp variations from minute to minute. Several minutes after the burn, the heart rate became rapid and regular and remained so throughout the experiment. The increased blood pressure was maintained for many hours, declining gradually to reach the original level at ten hours.

The average initial blood pressure in 14 spinal cats was 91 mm. Hg. During the period of the burn, in contrast to the experiments on normal cats, the arterial pressure fell sharply, an average of more than

30 mm. Hg as shown in Fig. 1. During and immediately following thermal trauma, the heart became irregular, and slowed in every case, the average heart rate noted at the termination of the burn being 91 beats per minute (54 to 128). Within five to ten minutes after cessation of thermal trauma, the heart became and remained rapid and regular. The blood pressure rose gradually to the initial level in one and one-half hours and did not fall much below this level during the period of observation.

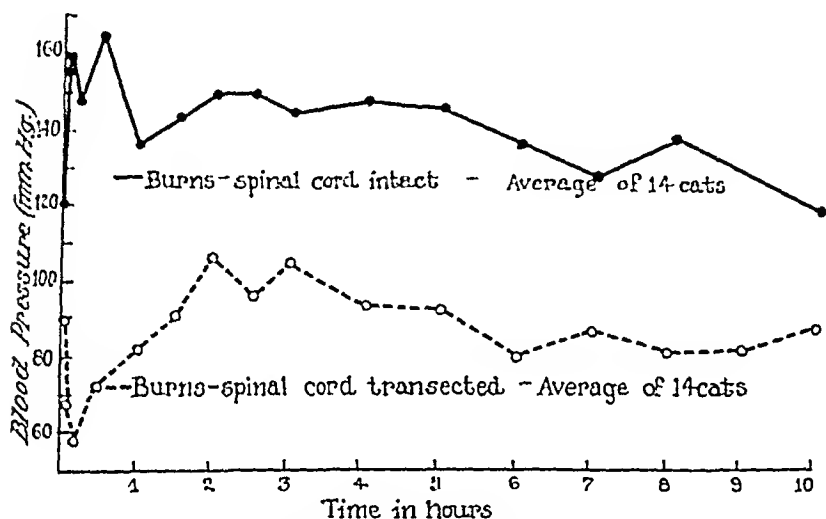


Fig. 1.—Changes in arterial pressure resulting from burns in control and spinal cats. All points are average values.

II. *Hemoglobin*.—In 24 control cats, the initial hemoglobin was 9.69 Gm. per 100 c.c. of blood. Hemoglobin increased sharply as a result of the burn; at thirty minutes the blood had concentrated 34.5 per cent (Fig. 2). After this initial hemoconcentration, hemoglobin continued to rise slowly, reaching a maximal increase of 44 per cent at eight hours. Hemoglobin determinations in 5 cats at twenty-six hours after the burn showed a fall of 25 per cent below the peak value.

The initial hemoglobin averaged 9.96 Gm. per 100 c.c. of blood in 25 spinal cats. Hemoglobin increased much less rapidly as a result of burns in spinal animals (Fig. 2). At thirty minutes, hemoconcentration reached a value of only 14.5 per cent and then increased gradually to reach a maximum of 32 per cent at seven hours. Hemoconcentration in 5 cats twenty-three hours after thermal trauma was 4.1 per cent below the peak value.

No marked change in hemoglobin during the same period was noted in spinal animals which were not subjected to thermal trauma (Fig. 2). At thirty hours, in these experiments, the average hemoconcentration was 9 per cent.

III. *Specific Gravity of Blood.*—The average initial specific gravity of whole venous blood in 24 cats measured by the falling-drop technique, using the heparin method described above, was 1.0471.

The sharp initial rise in specific gravity following thermal trauma in control cats and the slight further increase with time are shown in Fig. 3. The specific gravity of the blood increased an average of 0.0106 within twenty minutes after the burn and attained a maximal increase of 0.0127 at three hours. After a longer interval, the specific gravity tended to decrease considerably, falling at twenty-five hours to an average of 0.0066 below the peak value in several experiments.

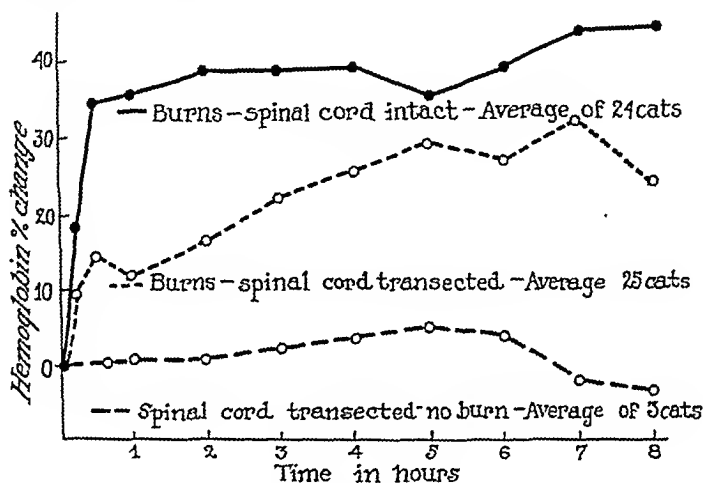


Fig. 2.—Percentage increase in concentration of the blood resulting from burns as demonstrated by hemoglobin determinations in control and spinal cats. All points are average values.

The blood concentrated more slowly and to a lesser extent following burns in 13 spinal cats (Fig. 3). Specific gravity increased only 0.0027 at twenty minutes and attained a maximal rise of 0.0066 at four hours. At twenty-four hours, the specific gravity was found to be 0.0003 below the maximum.

IV. *Respiration.*—The changes in respiratory rate resulting from burns in 14 control cats are shown in Fig. 4. The rate of respiration rose sharply during burning, and continued to rise for some time afterward, reaching a maximum of 36 per minute at two hours. Even at six hours, however, the respiratory rate averaged 29.5 per minute, considerably above the initial value.

In 12 experiments on spinal animals, the respiratory rate showed a greater rise following burns than in cats with the spinal cord intact (Fig. 4). Respiratory rate rose within fifteen minutes after initiation of thermal trauma to 42 per minute. The maximal respiratory rate of 47 per minute was noted at two hours, following which the rate of respiration declined.

30 mm. Hg as shown in Fig. 1. During and immediately following thermal trauma, the heart became irregular, and slowed in every case, the average heart rate noted at the termination of the burn being 91 beats per minute (54 to 128). Within five to ten minutes after cessation of thermal trauma, the heart became and remained rapid and regular. The blood pressure rose gradually to the initial level in one and one-half hours and did not fall much below this level during the period of observation.

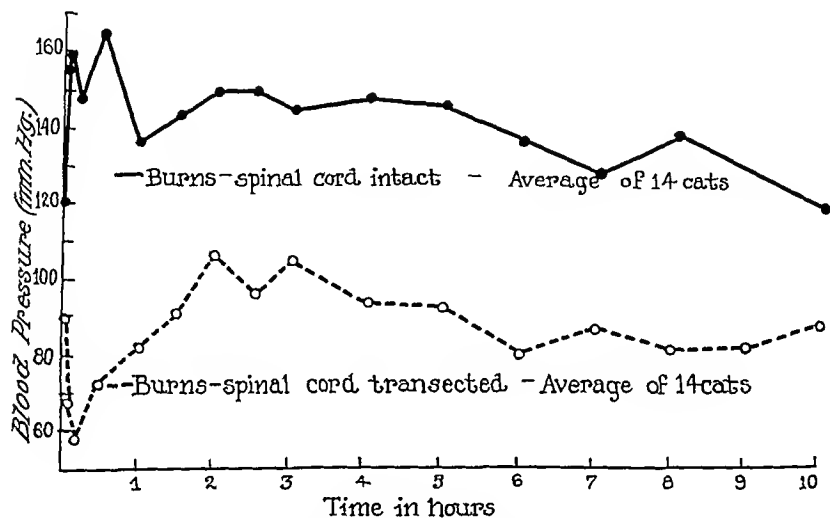


Fig. 1.—Changes in arterial pressure resulting from burns in control and spinal cats. All points are average values.

II. *Hemoglobin*.—In 24 control cats, the initial hemoglobin was 9.69 Gm. per 100 c.c. of blood. Hemoglobin increased sharply as a result of the burn; at thirty minutes the blood had concentrated 34.5 per cent (Fig. 2). After this initial hemoconcentration, hemoglobin continued to rise slowly, reaching a maximal increase of 44 per cent at eight hours. Hemoglobin determinations in 5 cats at twenty-six hours after the burn showed a fall of 25 per cent below the peak value.

The initial hemoglobin averaged 9.96 Gm. per 100 c.c. of blood in 25 spinal cats. Hemoglobin increased much less rapidly as a result of burns in spinal animals (Fig. 2). At thirty minutes, hemoconcentration reached a value of only 14.5 per cent and then increased gradually to reach a maximum of 32 per cent at seven hours. Hemoconcentration in 5 cats twenty-three hours after thermal trauma was 4.1 per cent below the peak value.

No marked change in hemoglobin during the same period was noted in spinal animals which were not subjected to thermal trauma (Fig. 2). At thirty hours, in these experiments, the average hemoconcentration was 9 per cent.

and 20.6 per cent if one considers the median values. There is thus a possible small increase in survival after cord transection.

Of special interest is the fact that a number of animals died during or immediately after burning: 9.3 per cent of all control cats and 6.9 per cent of the spinal cats. In all of these cases the respiration stopped suddenly during the burn, the heart was slow and irregular, and artificial respiration did not result in recovery, although the heart continued to beat for some time. The blood pressure was very low at the time respiration stopped in spinal animals. The local fluid loss in the burned limb averaged 1.15 per cent of the body weight, and hemoglobin was only 5 per cent above the initial level at the time of death. In one instance, respiration stopped during thermal trauma and after removal of the flame for one minute, spontaneous respiration was resumed; continuation of the burn for a total of fifteen minutes did not cause a further crisis and the animal survived for ten hours.

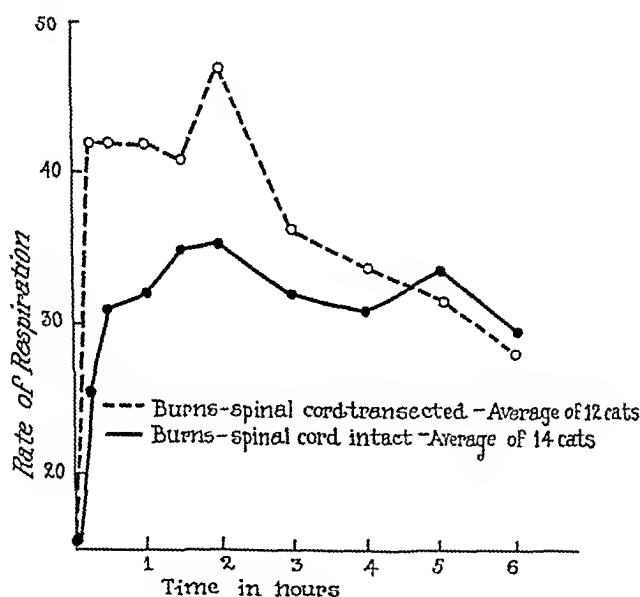


Fig. 1.—Changes in respiratory rates following burns in control and spinal cats. All points are average values.

VII. *Local Fluid Loss.*—The average local fluid loss in the burned limb in 14 control cats was 2.5 per cent of the body weight. The average maximal hemoglobin increase was 45 per cent. The local fluid loss did not correlate very closely with survival time or hemoglobin concentration. In 10 cats sacrificed at an average time of fourteen and one-tenth hours following the burn (six and one-half to thirty-four hours), the local fluid loss was 2.9 per cent of the body weight and the average maximal hemoglobin increase was 42.4 per cent. On the other

V. *Temperature*.—The rectal temperature before the burn averaged 98° F. in 29 control cats. The average increase in body temperature recorded immediately after the burn was 4.2° F. The temperature began to fall soon after thermal trauma was terminated and continued to fall progressively.

In 30 spinal cats, body temperature averaged 97° F. before the burn with a range from 92 to 100° F. Immediately after thermal trauma, the rectal temperature increased an average of 4.2° F. to 101.2° F. (92.6 to 110° F.).

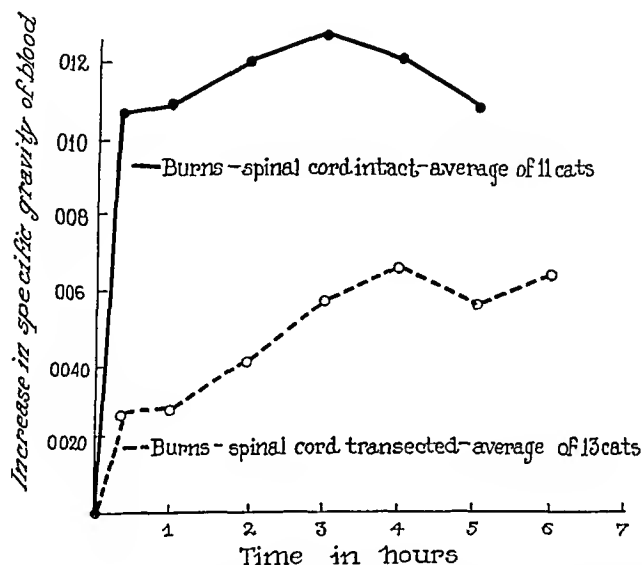


Fig. 3.—Hemoconcentration following burns as demonstrated by measurements of the specific gravity of the blood by the falling drop technique in control and spinal cats. All points are average values.

VI. *Survival*.—The extreme variability of survival time after burning has made a quantitative study of the effect of spinal transection difficult. Survival was studied in selected cats in which blood pressure was not recorded and no surgery was performed on the neck. Also, cats which died acutely within one hour of burning were not considered in the analysis of survival. In all of these experiments, one hindlimb was burned for fifteen minutes. In 24 normal cats, survival ranged from one and one-half to eighty hours. The average survival in this series was thirty-two and one-half hours and the median survival thirty-four hours. In 19 cats with the spinal cord transected at the eleventh thoracic segment, the average survival following the burn was forty hours, the median forty-one hours, and the range was ten to seventy-five hours. The apparent increased survival following burns in the spinal cats was 23.1 per cent if one considers the average values

TABLE I  
GROSS PATHOLOGY OF EXPERIMENTAL BURNS

		SPINAL CORD INTACT (38 CATS)	SPINAL CORD TRANSECTED (35 CATS)	ACUTE DEATHS (5 CATS)
Lungs	Slight congestion	31%	63%	40%
	"	13%	11%	40%
	"	16%	11%	20%
	Total congestion	60%	85%	100%
Kidneys	Slight congestion	16%	20%	20%
	"	10%	37%	
	"	34%	20%	
	Total congestion	60%	77%	
Urinary bladder	Urine			
	Normal	21%	22%	100%
	Bloody	79%	78%	
	Submucous hemorrhage in bladder	10%	30%	
Heart	Subendocardial hemorrhage left ventricle			
	Slight	16.0%	28%	20%
	Moderate	2.6%	14%	
	Marked	16.0%	11%	20%
	Total	34.6%	53%	40%
	Clot in right ventricle	30.0%	31%	40%
	Clot in left ventricle	8.0%	11%	20%
	Bloody pericardial fluid	2.6%	2.8%	
	Clear pericardial fluid		2.8%	10%
Stomach and duodenum	Submucous hemorrhage, pylorus	8.0%	2.8%	
	Hemorrhage and ulcer, pylorus	2.6%	5.6%	
	Ulcer, pylorus		11.0%	
	Submucous hemorrhage, duodenum	10.0%	5.6%	20%
	Ulcer, duodenum	2.6%	2.8%	
	Total	23.2%	27.8%	
Adrenals	Hemorrhage	16.0%	8.6%	
	Congestion	2.6%	8.6%	
Liver	Punctate hemorrhages	0	14%	20%

## DISCUSSION

Despite the fact that one of the established procedures in the therapy of clinical burns is the administration of morphine for the relief of pain, very little attention has been paid to the role of a nervous factor in shock following thermal trauma. In his review on burns, Harkins<sup>5</sup> declared: "A purely nervous theory of causation of shock and death in burns is not generally held. This is quite contrary to the case with traumatic shock in general where many workers support a purely nervous theory." Wilson<sup>6</sup> noted that nothing is known about the influence of noxious nerve impulses in burn shock. However, the general clinical impression has been that relief of pain in burns is of value in combating shock.<sup>2</sup>

The only previous experimental study of a nervous factor in burns was reported in 1858 by Brown-Sequard.<sup>10</sup> He stated in a lecture in England: "In two cases, on animals in which the trunks of the sciatic



hand, in 4 cats which died from the burn in an average of ten and two-tenths hours (one to twenty-one hours), local fluid loss was 1.6 per cent of the body weight and the maximal hemoglobin increase was 55 per cent.

Local fluid loss in the burned limb was 1.5 per cent of the body weight in 14 spinal cats and the maximal hemoglobin increase 25 per cent. Seven of these cats, which were sacrificed in an average of nineteen hours (eleven to thirty hours) had a local fluid loss of 2.2 per cent, and a maximal hemoglobin increase of 24 per cent. In 7 other cats which died from the burn in an average of ten and six-tenths hours (ten minutes to sixteen hours), the local fluid loss was only 0.96 per cent, while the maximal hemoglobin increase was 26 per cent.

*VIII. Pathology.*—Observations on gross pathology were made after burns on 38 control cats and 35 spinal cats. In the burned hindlimb, the skin was contracted, dry and leathery, and split in one or more places. The subcutaneous tissue was markedly edematous. The superficial veins were all thrombosed and contained a dark brown, semisolid coagulum.

The data on pathology of the internal organs are summarized in Table I. It is noteworthy that a greater percentage of the spinal cats showed pathologic changes in the lungs, kidneys, urinary bladder, heart, stomach and duodenum, and liver. The lesions were, however, no more severe in the spinal animals. As will be evident from the table, most of the cats showed pulmonary and renal congestion and dark, bloody bladder urine. Other frequent lesions were subendocardial hemorrhages in the left ventricle, clots in the right ventricle, and acute hemorrhage or ulceration in the pylorus or duodenum. The liver was not infrequently discolored, soft and friable; the spleen large, dark purple, and congested. In a number of cases, the myocardium had a violet tinge and appeared to be degenerating. In several cats, the anterior mediastinum was hemorrhagic.

Emphasis should be placed on the fact that pericardial effusion was a very infrequent finding. Pleural effusion or ascites was never observed in any of the animals. The intestines were not edematous, congested, or distended with fluid and in most instances appeared quite normal. The low incidence of adrenal pathology is also worthy of mention.

In 5 cats which died acutely during or immediately following thermal trauma, the pathology is listed in Table I. All showed pulmonary congestion; 2 moderate and 1 marked congestion. The urine was normal, the kidneys little affected. The spleen was large, dark, and congested. There was a good deal of cardiac pathology. In 2 instances, the brain was carefully examined but there was no pathology to account for the sudden arrest of respiration.

from two to five hours after the burn in the spinal cat, there must be a nonnervous pressor influence during this period which contributes to the sustained rise in blood pressure in the normal animal. The close correspondence of the general directions of the arterial pressure curves of normal and spinal animals after the first hour following burns is also of interest (Fig. 1).

The most interesting effect of elimination of the nervous factor in burns is the marked decrease in hemoconcentration demonstrable by both hemoglobin and blood specific gravity measurements. Hemoeconcentration is considerably less and also increases more slowly in burned spinal cats (Figs. 2 and 3). Local fluid loss in the burned area is also less in spinal animals. The increased hemoconcentration resulting from the nervous factor may perhaps be accounted for by the higher arterial pressure, reflex contraction of the spleen, vasoconstriction, and adrenalin secretion. The influence of a reflex rise in arterial pressure on blood volume is negligible in normal animals, as shown by Greger-son,<sup>13</sup> but may be greater in burns due to the capillary injury. A higher filtration pressure would explain the greater local fluid loss in the burned animal with intact spinal cord. Animals with the spinal cord transected at the eleventh thoracic segment and no burns showed a negligible and very gradual hemoconcentration (Fig. 2). Treat<sup>14</sup> has demonstrated that acute transection of the spinal cord at the eighth cervical segment in cats, with a fall in blood pressure of 40 per cent, resulted in an increase of plasma volume of only 5 per cent. Contraction of the spleen is probably also important in exaggerating the hemoconcentration following burns in control animals. Keeley, Gibson, and Pijoan<sup>9</sup> reported increases of circulating erythrocyte volumes of 59.5, 24.6, and 22.3 per cent in normal dogs, and decreases of 27.8, 13.1, and 7.8 per cent in splenectomized dogs, as a result of extensive burns. There was also a smaller rise in hemoglobin in the splenectomized dogs. On the other hand, they reported a greater decrease of plasma volume and of total blood volume in the burned splenectomized animals.

While the survival time following the burn was apparently increased slightly by preliminary spinal transection, one cannot be certain that this is a valid conclusion, considering the extreme variation in the survival data.

#### CONCLUSIONS

1. (a) In control cats, thermal trauma results in an immediate rise in blood pressure which is sustained for many hours. (b) In spinal animals, there is a temporary fall in blood pressure followed by a lesser rise as a result of the burn.
2. Hemoconcentration following a burn is less in spinal animals.
3. Spinal transection decreases local fluid loss in the area of the burn.
4. The increase in respiratory rate resulting from the burn is greater in spinal animals.

and crural nerves in one limb had been divided as high as possible, I have not found a state of marked congestion in any viscera, three days after I had carbonized this limb from the toes to the middle of the thigh." He also found an absence of visceral pathology following burns of one leg in animals in which the spinal cord had been divided at the third or fourth lumbar segment. On the other hand, visceral congestion was observed following burns in animals with the spinal cord transected at the third thoracic segment. "From these experiments and the preceding, it results that it is, in a great measure, by a reflex action of the spinal cord, that burns produce their deadly influence on the viscera." Brown-Sequard also recognized the importance of other factors: "Of course, it is not by reflex action only that some of the phenomena mentioned in this lecture are produced. . . . In a case of extensive burns, for instance, there are several circumstances which contribute to the production of the visceral alterations. . . ."

In the present study, it has been possible to demonstrate a nervous factor in burn shock even under surgical barbiturate anesthesia. The type of experimental procedure employed necessitated the use of surgical anesthesia in this investigation. While it is difficult to predict the exact significance of the nervous factor in the unanesthetized animal, it is probable that afferent nerve impulses exert a more potent influence under those conditions. While the nervous factor may not be the major factor in determining a lethal outcome, it nevertheless plays a significant contributory role in the shock which follows thermal trauma.

Transection of the spinal cord at the first lumbar segment effectively prevents the initial and to some extent the sustained rise in blood pressure which results from thermal trauma. Since practically the entire sympathetic vasomotor pathway remains intact when the spinal cord is divided at this level, spinal transection must eliminate the rise in arterial pressure by cutting off afferent nerve impulses from the burned area presumably activating the sympatheticoadrenal system. It is noteworthy that stimulation of superficial nerve endings in the hindlimb by a burn produces a reflex rise in arterial pressure, while stimulation of the nerve endings in deeper tissues by fracture of the long bones elicits a fall in blood pressure.<sup>3</sup> Since both pressor and depressor fibers run together in the large nerve trunks, one would expect on stimulation of such nerves that the opposing pressor and depressor influences would more or less neutralize one another. These facts may help to explain the failure of many investigators<sup>12</sup> to produce shock by experimental stimulation of nerves.

An initial sharp fall in arterial pressure during and following thermal trauma occurs in spinal animals; this fall is related to toxic and fluid loss factors and is ordinarily masked by the pressor reflex. Since the blood pressure rises slightly above the original level during the period

# HEMORRHAGIC CYSTS OF THE LUNG: REPORT OF TWO CASES IN WHICH MARSUPIALIZATION WAS DONE

HOWARD K. GRAY, M.D., AND IRA C. SKINNER,\* M.D.,  
ROCHESTER, MINN.

(From the Division of Surgery, Mayo Clinic)

FONTANUS wrote to Cl. Plempius, in 1638, the first recorded description of a patient who had a presumed congenital cyst of the lung. This appeared in a report (*De Pulmonibus*) by Thomas Bartholinus of three such cases which were published in 1687 in Malpighius' *Opera omnia*. Excerpts from the translation by Oughterson and Taffel are very interesting:

"A new case, and a rare one in mankind, of a boy without the ordinary lung—a case observed by N. Fontanus and favorably commented upon by ourselves—amply confirms the new observation of Malpighius. . . . The four-year-old boy died, brought to his end by marasmus. Out of interest in the matter I dissected the body, observing that the liver was above the ordinary size. It had an abscess near the vena cava, which was covered with pus all around about the humped portion; a spleen of good color, and unaffected; no omentum or at least none was readily visible. And strange to relate, there were no lungs, but in their place was a membranous vesicle filled with air. This vesicle was provided with small veins and arose from the rough artery [trachea] itself; the vesicle seemed to carry the cooling effect to the heart. Fontanus wrote this to Cl. Plempius on December 20, 1638. He in turn, in his answer of December 29, judged the membranous vesicle to have occupied the place of a lung, since it could receive outside air for cooling the heart by virtue of the fact that it started from the rough artery. But because it did not furnish enough air to the heart, and because the heart could not easily enough be cleansed of its soot, the learned Plempius suspects that therefore the youth fell into this marasmus, the heat of the heart being too intense and almost burning up the body."

Koontz in 1925 called the attention of American physicians to the disease in question by his review of 108 reports of cases collected from the foreign literature, chiefly German. Sehenek, in July of 1937, was able to gather a total of 381 reports of cases from the world literature on the subject. Wood<sup>10</sup> in August of the same year reported an additional forty-eight cases in which the patients had been seen at the Mayo Clinic. Since that time numerous isolated reports of cases and groups of cases have appeared in various journals.

## ETIOLOGIC ASPECTS

The obscurity of the cause of cystic disease of the lung is indicated by the number of theories evolved to explain its genesis. The scope of

\*Fellow in Surgery, The Mayo Foundation.  
Received for publication July 23, 1941.

5. There is no significant difference in visceral pathology in control and spinal animals following burns.

## REFERENCES

1. Crile, G. W.: *An Experimental Research into Surgical Shock*, Philadelphia, 1899, J. B. Lippincott Co.
2. O'Shaughnessy, L., and Slome, D.: *Etiology of Traumatic Shock*, *Brit. J. Surg.* 22: 589-618, 1935.
3. Lorber, V., Kabat, H., and Welte, E. J.: *The Nervous Factor in Traumatic Shock*, *Surg., Gynec. & Obst.* 71: 469-477, 1940.
4. Freedman, A. M., and Kabat, H.: *The Pressor Response to Adrenalin in the Course of Traumatic Shock*, *Am. J. Physiol.* 130: 620-626, 1940.
5. Volpitta, P. P., Woodbury, R. A., and Hamilton, W. F.: *Direct Arterial and Venous Pressure Measurements in Man as Affected by Anesthesia, Operation and Shock*, *Am. J. Physiol.* 128: 238-245, 1940.
6. Wilson, W. C.: *The Cause and Treatment of the Lethal Factors in Burns*, *Edinburgh M. J.* 48: 85-93, 1941.
7. Scudder, J.: *Shock: Blood Studies as a Guide to Therapy*, Philadelphia, 1940, J. B. Lippincott Co.
8. Harkins, H. N.: *Recent Advances in the Study of Burns*, *SURGERY* 3: 420-465, 1938.
9. Kceley, J. L., Gibson, J. G., Jr., and Pijoan, M.: *The Effect of Thermal Trauma on Blood Volume, Serum Protein, and Certain Blood Electrolytes: An Experimental Study of the Effect of Burns*, *SURGERY* 5: 872-893, 1939.
10. Brown-Sequard, E.: *Course of Lectures on the Physiology and Pathology of the Central Nervous System. Lecture X. The Influence of the Nervous System Upon Nutrition, Secretion and Animal Heat; With Remarks on the Importance of the Knowledge of This Influence for the Diagnosis and Treatment of Disease*, *Lancet* 2: 545-547, 1858.
11. Harkins, H. N.: *Experimental Burns, I. The Rate of Fluid Shift and Its Relation to the Onset of Shock in Severe Burns*, *Arch. Surg.* 31: 71-85, 1935.
12. Mann, F. C.: *The Peripheral Origin of Surgical Shock*, *Bull. Johns Hopkins Hosp.* 25: 205-212, 1914.
13. Gregerson, M. L.: *Some Effects of Reflex Changes in Blood Pressure on Plasma Volume*, *Am. J. Physiol.* 129: 369, 1940.
14. Treat, A. E.: *Acute Effects of Spinal Cord Section Upon the Plasma Volume and Blood Pressure of Cats Under Ether Anesthesia*, *Am. J. Physiol.* 134: 310-318, 1941.

meet the different problems that arise in such management. It is generally agreed that those cysts which are accidentally discovered and which are producing no symptoms require no treatment. The crises of dyspnea and cyanosis which occur among young children and infants as a result of large balloon cysts may necessitate repeated aspiration of air from the cyst. Pearson has reported a case in which an 18-month-old child was cured by repeated aspiration. Croswell and King have written of a patient who was benefited by repeated aspiration and, on one occasion, the injection of radiopaque oil into the cyst.

Miller and Lillienthal have inserted one-way "flapper-valve" tubes through the thoracic wall in an effort to prevent the recurrence of increased pressure within the cyst. Bronchoscopic aspiration followed by the injection of iodized oil has been beneficial to a few patients. Wood<sup>18</sup> reported a case in which a patient remained in good health for ten years after thoracotomy and cauterization of the bronchial openings into the cyst. Results of cauterization of the bronchus leading to the cyst through the bronchoscope have been inconstant. Oughterson and Taffel think that this procedure is contraindicated, because it may only partially occlude the bronchus and thus make the condition worse by prevention of the escape of trapped air from the cyst. They recommend introduction of a catheter into the cyst of which the walls have been previously scarified. Negative pressure is then established in the hope of re-expansion of the lung, which will adhere to the thoracic wall. The treatment of choice in cystic disease of the lung would of course be removal of the affected tissue. This may be accomplished by either lobectomy or excision of the cyst. Harrington<sup>2</sup> successfully removed a cystic azygous lobe from the posterior portion of the mediastinum. He also reported<sup>6</sup> on a young married woman, 19 years old, from whom he removed a large intrathoracic cyst which contained clotted blood. She remained well after this procedure. Sauerbruch was able to extirpate the cyst or to perform lobectomy for six patients. One of these died of postoperative shock; the rest were cured. Lee and Harris found reports by Miller, Zdansky, Melchior, Braeuning and Clairmont on patients from whom such cysts were removed in toto with gratifying results.

When patients are encountered from whom removal of the cyst is impossible, marsupialization may result in benefit. Eloesser operated on a male student, 20 years old, who had suffered from what was thought to be chronic empyema for eleven years. At the first operation multiple infected cysts of the left lower lobe of the lung were uncapped and marsupialized. At a second operation a large air-containing and fluid-containing cyst of the upper lobe was drained. The third procedure constituted removal of the sacculated lower lobe. The patient made a good recovery and, except for development of a minute bronchial fistula, seemed well thereafter, although he did not gain weight. The upper cystic cavity remained empty and produced no symptoms.

the present paper is too limited to enter into such an inquiry. Suffice it to say that cystic disease of the lung has been attributed to congenital malformations, neoplastic changes, dilatation of the lymphatic vessels, congenital syphilis, congenital bronchiectasis, inflammation within the bronchi during intra-uterine development, bronchopneumonia, and other conditions. It is reasonable to suppose, with Oughterson and Taffel, that pulmonary cysts are similar to cysts of other parenchymatous organs of the body and that, like such cysts, they may be congenital, infectious, mechanical, or neoplastic in origin.

#### SYMPTOMS

Unfortunately, there are no symptoms which are characteristic of cysts of the lungs. Indeed, a large pulmonary cyst in many cases may be discovered only at post-mortem examination or on the occasion of routine roentgenologic examination of the thorax. However, most authors, such as Taylor, Wood,<sup>18, 19</sup> Schenck, King and Harris and others, have agreed that among children and infants recurrent attacks of dyspnea and cyanosis should make the physician suspect cystic disease of the lungs. Among adult persons the disease usually is manifested because of some complication. If the cyst becomes infected (or if cysts become infected) fever, cough, and expectoration result. Rupture of an air cyst into the pleural space results in formation of the clinical picture of spontaneous pneumothorax. Cysts which have a valvelike mechanism may enlarge sufficiently to produce symptoms arising from compression and distortion of the mediastinal structures. Hemoptysis is a frequent symptom. This symptom, together with the observation of cavitation in the thoracic roentgenogram, has led to the sending of many patients into a sanatorium with the diagnosis of "tuberculosis." Three of Hennell's eight patients gave as their chief symptom recurrent episodes of hemoptysis. Hemoptysis was a prominent symptom in fifty-two of 381 reports of cases collected by Schenck.

#### DIAGNOSIS

The diagnosis of cystic disease of the lung can be made only after satisfactory roentgenologic study of the thorax has been made. In addition to these, bronchoscopic examination, the injection of radio-paque oil, and performance of diagnostic pneumothorax may be necessary.

Wood<sup>18</sup> emphasized the extreme difficulty of distinguishing fluid-containing cyst from (1) thoracic tumor, (2) pulmonary abscess, (3) empyema, (4) dermoid cyst, and (5) echinococcus cyst. At times the distinction between a fluid-containing cyst and a solid tumor can be made only by exploratory thoracotomy.

#### TREATMENT

The proper management of patients who have cystic disease of the lung is extremely difficult and various methods have been devised to

(Fig. 1*A* and *B*). These were thought to be independent of the large vessels. Bronchoscopic examination revealed some degree of compression of the left lower lobe bronchus, caused apparently by an extrabronchial tumor mass. Tissue removed from this region was inflammatory in nature. Results of repeated examinations of sputum were entirely negative for tuberculosis, and the electrocardiogram disclosed nothing abnormal. The urea measured 14 mg. per 100 c.c. of blood and the sedimentation rate was 21 mm. per hour. Urographically, there was no evidence of polycystic disease of the kidneys. The rest of the routine laboratory examinations, including the flocculation test for syphilis, gave negative results.

A diagnosis of intrathoracic tumor of indeterminate nature was made and surgical exploration was advised.



Fig. 1 (Case 1).—Two large circumscribed shadows involving the greater part of the left lung and the left half of the thoracic cavity; *A*, anteroposterior view; *B*, lateral view.

On February 20, 1940, thoracotomy was performed with the patient under the influence of anesthesia produced by cyclopropane administered intratracheally. The incision was made on the left, along the eighth interspace posterolaterally and extending below the angle of the scapula (Fig. 2*A*). The eighth and ninth ribs were cut near their angles and an incision was made between them into the pleural cavity. On opening the pleural space two large globular masses were seen (Fig. 2*B*). These were separated partially from the parietal pleura with some difficulty. The lower tumor seemed definitely cystic and a needle was inserted into it. Thin, brown, bloody material was obtained. The upper mass seemed to be more solid in consistency and the aspiration needle produced thick, brown, chocolate-like material. This mass was then incised and approximately 400 c.c. of the thick, chocolate-like material was evacuated from it. It was found to be a cyst, the lining of which was perfectly smooth. The cyst was roughly round and was approximately 20 cm. in diameter. It did not communicate with the lower cyst; the lower cyst was therefore incised. The lower cyst contained thin, sero-anguineous fluid, and was approximately the same size as the superior cyst. It seemed impossible to remove these structures because they evidently arose in the substance of the lung. The lung itself was markedly compressed medially and anteriorly. Performance



Neuhof reported a case in which a woman 30 years old was thought to have empyema. At operation a well-defined hemispheric bulge of the right lower lobe was noted. On the assumption that this bulge was caused by an abscess of the lung, this part of the lobe was packed off from the remainder of the pleural cavity and the wound was packed. Pus obtained by aspiration proved to be sterile. At a second operation the lung was entered and a large amount of pus was evacuated from a smooth-walled cyst which communicated with a bronchus. The cyst was lined with ciliated epithelium of bronchogenic character. The postoperative course of the patient was satisfactory and at the time of Neuhof's report the cavity would hold only 10 to 15 c.c. of fluid.

Adams and Swanson recorded a case in which a 45-year-old woman had complained of a productive cough which she said had been present for five years. Roentgenologic study revealed a large fluid-containing and air-containing cyst of the right lung. A two-stage operation similar to the one previously described herein was performed. After drainage of the cyst, the productive cough disappeared. However, if the external opening of the cyst became occluded the patient would again begin to cough. The cavity failed to decrease in size during the period of observation of this patient.

We have two cases of our own, involving cysts of the lung, which we wish to present herein.

#### REPORT OF CASES

**CASE 1.**—A man 34 years old registered at the Mayo Clinic on January 30, 1940. He complained chiefly of dyspnea of seven months' duration. In July, 1939, while sitting quietly in a theater, he had experienced sudden severe substernal and epigastric pain associated with intense dyspnea. He had been rushed to a local hospital, where thoracentesis was immediately done. Several hundred cubic centimeters of bloody fluid were removed from the left hemithorax. After removal of this fluid the marked dyspnea subsided, but the patient failed to regain his former respiratory reserve. Further careful study revealed areas in the left part of the thorax which were interpreted as being aneurysmal sacs or neoplasms. In October, 1939, he was able to return to his work in a printing business, but he continued to experience pain in the left costovertebral region and began to cough up clots of old blood. This continued for six weeks. He remained dyspneic and the dyspnea occurred after slight exertion.

A review of this patient's history disclosed nothing of significance in relation to his illness, except for the occurrence of an attack of "pleurisy" when he was 18 years old. This attack had consisted of slight pain in the left portion of the thorax which had inconvenienced him for only a short time.

On examination the patient was found to weigh 138 pounds (62 kg.). His normal weight was 150 pounds (68 kg.). The systolic blood pressure was 150, and the diastolic pressure was 100, expressed in millimeters of mercury. A small adenoma of the thyroid gland was present. Litten's sign was absent on the left and percussion revealed a region of dullness extending from the fourth thoracic vertebra inferiorly on the left side of the thorax. Breath sounds were decreased over this region. Roentgenologic examination demonstrated two large circumscribed shadows involving the greater part of the left side of the thoracic cavity

day, at which time he began to have a septic type of fever. At subsequent thoracentesis a collection of fluid was found anterolaterally on the left. The *Streptococcus haemolyticus* and the *Staphylococcus aureus* were cultured from this fluid. The patient received 2-sulfanilamido-4-methylthiazole (sulfamethylthiazole) with benefit. Examination of the lower cystic cavity on the fourteenth postoperative day revealed a bronchial opening in the depths of the cavity. Since the septic fever continued, it seemed necessary to institute open drainage of the empyema cavity. This was accomplished by removal of a portion of the fifth and sixth ribs, anterolaterally. The patient then began to improve rapidly and he was able to leave the hospital on the thirty-first postoperative day. Three months later his physician at his home reported that the patient was feeling well. The roentgenograms, which the patient's physician was kind enough to send to us, showed considerable clearing of the exudate and diminution of the pleuritis which had been present at the last time a roentgenogram had been made of the patient's thorax at the clinic. The right portion of the diaphragm was elevated by pleuritic adhesions. The cystic cavities were somewhat decreased in size.

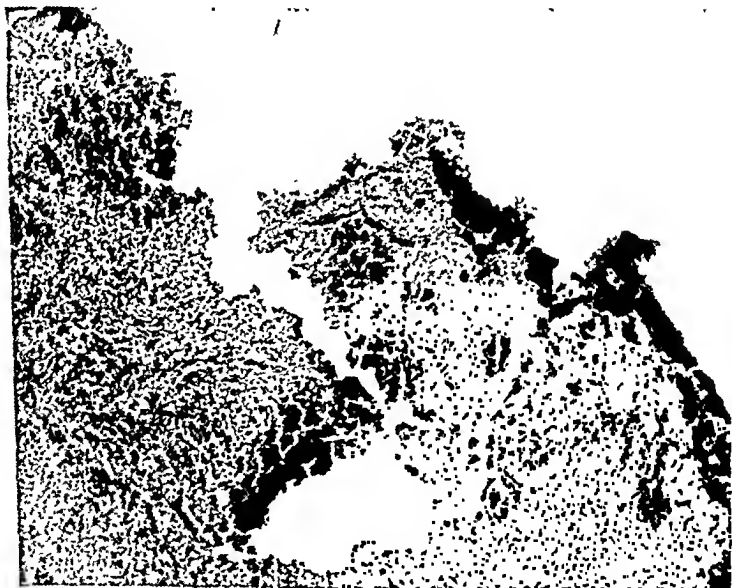


Fig. 3 (Case 1)—Section of the wall of a hemorrhagic cyst of the lung. There was no specific lining to this cyst. The wall was composed of inflammatory fibrous tissue, and the surface was covered with blood (hematoxylin and eosin  $\times 15$ ).

CASE 2. A man 26 years old registered at the clinic on January 27, 1911. He stated that he had been accepted for military service on December 27, 1910. While he was hunting a week later he was running fast in a high, cold wind and the next day he coughed up blood. He also had some pain in the left shoulder. Since that time he had been coughing up old blood and it had been necessary for him to stay in a local hospital for two weeks. He gave a history of having had pleurisy on the left side five years prior to his registration at the clinic.

On examination he was found to have a blood pressure of 125, systolic, and 80, diastolic, expressed in millimeters of mercury. His temperature was 98.6° F. (37° C.). Examination of his thorax showed the breath sounds to be decreased

of pneumonectomy was considered to be impossible because of the number of dense adhesions existing between the parietal and visceral pleura. It was therefore decided to marsupialize the cystic cavities. They were made to communicate and the edges were brought up to the parietal pleura and attached throughout their circumference with multiple interrupted catgut sutures to the soft tissues of the thoracic wall (Fig. 2C). Approximately 8 cm. of the eighth and ninth ribs were

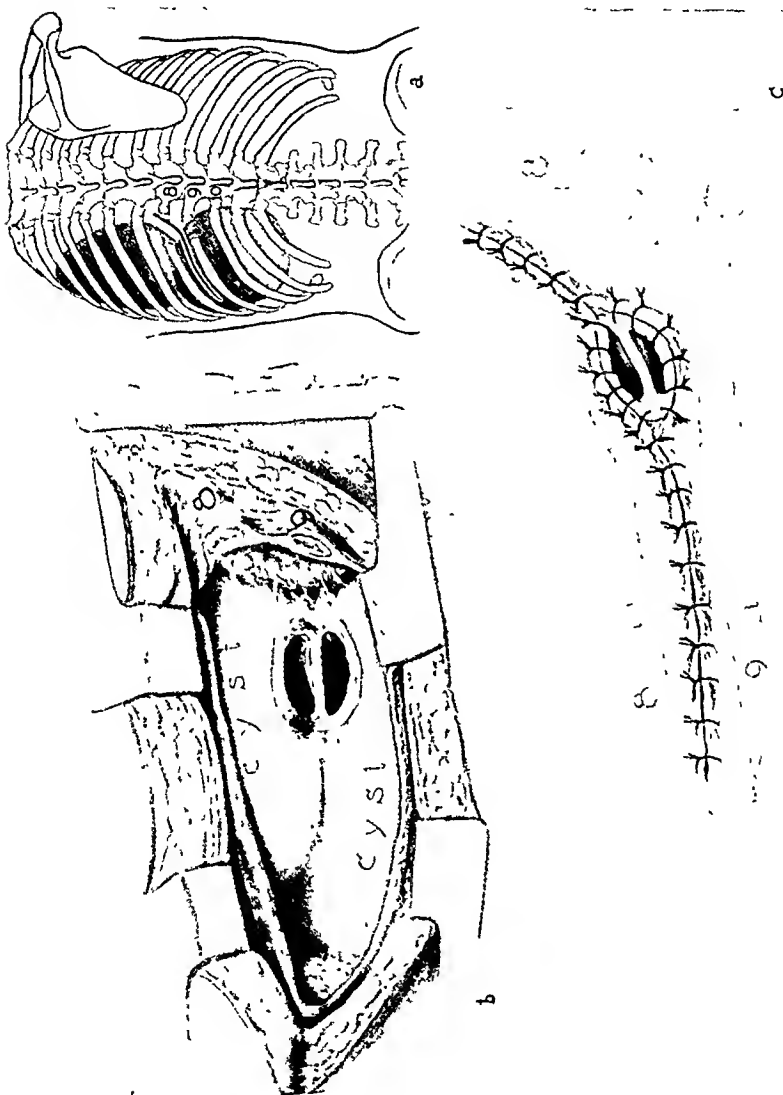


FIG. 2 (Case 2).—Surgical procedure involved in marsupialization of two hemorrhagic cysts of the left lung. A, an incision was made along the eighth interspace on the left, posteriorly; B, partial resection of the eighth and ninth ribs near their angles; C, two large independent hemorrhagic cysts have been made to communicate and marsupialization of the two cystic cavities has been accomplished.

removed to permit this procedure (Fig. 2C). The cystic cavities were then packed with petrolatum gauze. A portion of the cyst wall was removed for microscopic examination and proved to be fibrous hemorrhagic inflammatory tissue with deposition of hemosiderin (Fig. 3).

The patient was returned to his room in excellent condition and was immediately placed in an oxygen tent. His course was not unusual until the fifth postoperative

the space occupied by the cyst would be obliterated. It was impossible to marsupialize and drain the cyst in the region in which exploration had been carried out, because of the scapula. Consequently, a stab wound was made in the posterior

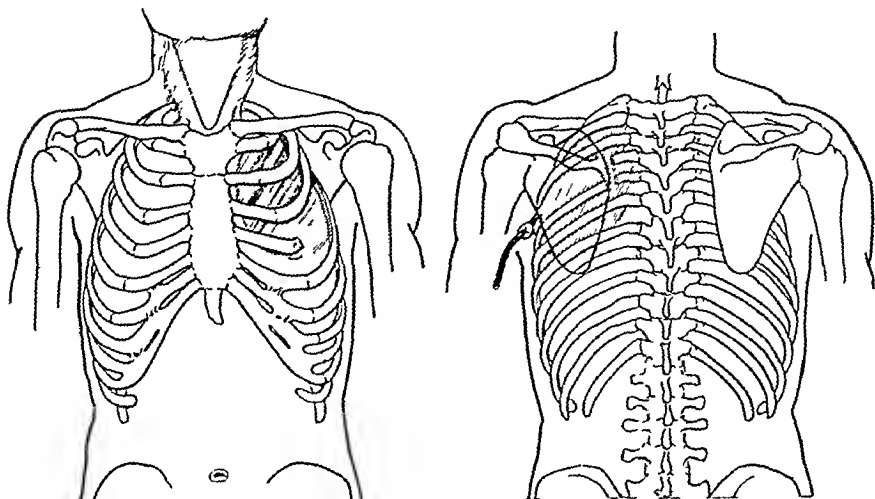


Fig. 5 (Case 2).—Representation of the surgical procedure involved in marsupialization of a hemorrhagic cyst of the left lung



Fig. 6 (Case 2).—Section of the wall of a hemorrhagic cyst of the lung; the predominant feature is the fibrous tissue. Inflammatory cells are evident around the vessels (hematoxylin and eosin  $\times 160$ ).

axillary line overlying the lateral portion of the fourth rib, which had been removed from the angle to this particular point (Fig. 5). The cystic structure was then opened, and a large quantity of old, black, clotted blood was removed. An opening approximately 3 cm. in length was made and the edges were brought up to the

in the upper part of the thorax on the left and there was marked dullness over the same area as far down as the third rib. A diagnosis of cyst of the lung had been made previously, elsewhere.

Urinalysis disclosed a specific gravity of 1.010. The reaction was acid. Pyuria of grade 1 (on the basis of 1 to 4) was present. The content of hemoglobin was 12.5 Gm. per 100 c.c.; erythrocytes numbered 4,060,000, and leucocytes 9,000, per cubic millimeter of blood. A differential count gave the following results: lymphocytes 15.5, monocytes 6.0, neutrophils 76.0, eosinophils 2.0, and basophils, 0.5. Anteroposterior and lateral roentgenograms of the thorax, made with a Bucky diaphragm, revealed a large, homogeneously dense tumor mass in the upper, posterior part of the thorax on the left, extending upward from just below the sixth rib to about the second rib (Fig. 4A and B). There was some erosion of the inferior margin of the fifth rib at the angle. The trachea was slightly displaced to the right. Results of Casoni tests for echinococcosis were negative. Reaction of the complement fixation test for echinococcosis was negative.



Fig. 4 (Case 2).—A dense tumor mass in the upper, posterior portion of the thorax on the left; A, anteroposterior view; B, lateral view.

A diagnosis of cyst of the upper lobe of the left lung, with secondary hemorrhage into the cyst, was made. Surgical treatment was advised and the patient underwent operation on January 28, 1941. A curved incision was made along the medial border of the scapula, extending from nearly the upper border of the scapula well laterally. Portions of the fourth and fifth ribs were removed near their angles. An intercostal incision was made in the fourth interspace and a large, rather indurated mass could be seen in the substance of the upper portion of the left lung. The left lung was densely adherent to the parietal pleura and could not be separated except in a very small region; it seemed to be densely attached medially and anteriorly, and it seemed that any attempt to remove it would have imposed more risk than was warranted. The aspirating needle was inserted into the cyst, and dark, bloody material was aspirated. It seemed advisable to drain the cyst, marsupialize the edges and hope that with re-expansion of the lung

6. Harrington, S. W.: Surgical Treatment of Intrathoracic Tumors. *Arch. Surg.* 19: 1679-1725, 1929.
7. Hennell, Herman: Cystic Disease of the Lung. *Arch. Int. Med.* 57: 1-17, 1936.
8. King, J. C., and Harris, L. C., Jr.: Congenital Lung Cyst. *J. A. M. A.* 108: 274-280, 1937.
9. Koontz, A. R.: Congenital Cysts of the Lung. *Bull. Johns Hopkins Hosp.* 37: 340-361, 1925.
10. Lillienthal, H.: Quoted by Oughterson, A. W., and Taffel, Max.
11. Miller, R. T.: Congenital Cystic Lung. *Arch. Surg.* 12: 392-405, 1926.
12. Neuhoof, Harold: Infected Congenital Cyst of Lung Improved by Marsupialization and Drainage. *Ann. Surg.* 87: 606-607, 1928.
13. Oughterson, A. W., and Taffel, Max: Pulmonary Cysts; Review of the Subject, With a Case Report. *Yale J. Biol. & Med.* 9: 77-100, 1936.
14. Pearson, E. F.: Cystic Disease of the Lungs (With Report of Eight Cases). *Illinois M. J.* 67: 28-37, 1935.
15. Sauerbruch: Quoted by Taylor, W. A.
16. Schenck, S. G.: Diagnosis of Congenital Cystic Disease of the Lung. *Arch. Int. Med.* 60: 1-21, 1937.
17. Taylor, W. A.: Congenital Cyst of the Lung. *Tr. West. S. A.* (1937) 47: 207-230, 1938.
18. Wood, H. G.: Congenital Cystic Disease of the Lungs; a Clinical Study. *J. A. M. A.* 103: 815-821, 1934.
19. Wood, H. G.: Congenital Cystic Disease of the Lung. *J. Thoracic Surg.* 6: 634-637, 1937.

deep fascia in the region of the stab wound. In this way, direct communication was established into the cystic structure laterally and anatomic closure of the original incision was made without drainage. Three large Penrose drains were left in the depths of the cavity of the cyst and a small portion of the edge of the cystic cavity was removed and sent to the laboratory for microscopic examination. The pathologists reported the cyst wall to contain fibrous and fatty inflammatory tissue (Fig. 6). Culture of the contents of the lung cyst (brain broth was used as a medium) revealed no growth of organism, nor were organisms grown on blood agar. Carbol-fuchsin stain of a smeared specimen revealed no acid-fast bacilli.

The patient withstood the operative procedure well. On the eleventh postoperative day he was allowed to sit in a chair for limited periods daily; he was afebrile and his general condition was excellent. Large quantities of black blood clot drained from the marsupialized region.

#### COMMENT

These cases were doubly interesting to us because it was impossible to make a correct diagnosis without the performance of thoracotomy and because of the unusual nature of the pathologic lesions found. In retrospect, it seems likely that the sudden shock and dyspnea experienced by the first patient represented extensive hemorrhage into the cystic cavities. He had had hemoptysis on only one occasion. The bronchi communicating with the cystic cavities must have become occluded and remained so until late in the patient's postoperative course. Hennell reported on a patient in whom a cyst containing blood was found at necropsy. Harrington<sup>6</sup> was able to remove in its entirety a cyst filled with blood. Although these are the only such cases of blood-filled cysts with which we are familiar, it would seem that such a complication would be a frequent one, the frequency of hemoptysis among patients who have such cysts being indicative of the delicacy of the vessels of the wall of the cyst. The bronchi leading to the cyst frequently are distorted and tortuous, so that it is not surprising that in the cases reported herein they should have become occluded and failed to drain the cyst properly.

In the cases presented herein, it was hoped that by marsupialization of the walls of the two cysts the uninvolved portion of the left lung could be made to re-expand and obliterate the cystic cavities.

#### REFERENCES

1. Adams, W. E., and Swanson, W. W.: Congenital Cystic Disease of the Lung; Review of the Literature and Report of Three Cases. *Internat. Clin.* 4: 205-220, 1935.
2. Croswell, C. V., and King, J. C.: Quoted by Oughterson, A. W., and Tuffel, Max.
3. Eloesser, L.: Congenital Cystic Disease of the Lung. *Surg., Gynec. & Obst.* 52: 747-758, 1931.
4. Fontanus, N.: Quoted by Oughterson, A. W., and Tuffel, Max.
5. Harrington, S. W.: The Surgical Treatment of Mediastinal Tumors; Removal of Cystic Azygos Lobe From Posterior Mediastinum. *Ann. Surg.* 98: 813-856, 1932.

6. Harrington, S. W.: Surgical Treatment of Intrathoracic Tumors. *Arch. Surg.* 19: 1679-1725, 1929.
7. Hennell, Herman: Cystic Disease of the Lung. *Arch. Int. Med.* 57: 1-17, 1936.
8. King, J. C., and Harris, L. C., Jr.: Congenital Lung Cyst. *J. A. M. A.* 108: 274-280, 1937.
9. Koontz, A. R.: Congenital Cysts of the Lung. *Bull. Johns Hopkins Hosp.* 37: 340-361, 1925.
10. Lillienthal, H.: Quoted by Oughterson, A. W., and Taffel, Max.
11. Miller, R. T.: Congenital Cystic Lung. *Arch. Surg.* 12: 392-405, 1926.
12. Neuhoof, Harold: Infected Congenital Cyst of Lung Improved by Marsupialization and Drainage. *Ann. Surg.* 87: 606-607, 1928.
13. Oughterson, A. W., and Taffel, Max: Pulmonary Cysts; Review of the Subject, With a Case Report. *Yale J. Biol. & Med.* 9: 77-100, 1936.
14. Pearson, E. F.: Cystic Disease of the Lungs (With Report of Eight Cases). *Illinois M. J.* 67: 28-37, 1935.
15. Sauerbruch: Quoted by Taylor, W. A.
16. Schenck, S. G.: Diagnosis of Congenital Cystic Disease of the Lung. *Arch. Int. Med.* 60: 1-21, 1937.
17. Taylor, W. A.: Congenital Cyst of the Lung. *Tr. West. S. A.* (1937) 47: 207-230, 1938.
18. Wood, H. G.: Congenital Cystic Disease of the Lungs; a Clinical Study. *J. A. M. A.* 103: 815-821, 1934.
19. Wood, H. G.: Congenital Cystic Disease of the Lung. *J. Thoracic Surg.* 6: 634-637, 1937.



# PARAVERTEBRAL THORACOPLASTY FOR THE TREATMENT OF PULMONARY TUBERCULOSIS

## A REPORT OF 146 CASES WITH FOLLOW-UP

GEORGE C. ADIE, M.D., LESTER C. HUESTED, M.D.,  
WILLIAM G. CHILDRESS,\* M.D., AND HORACIO E. PEREZ,\* M.D.,  
VALHALLA, N. Y.

THE object of this paper is to review the material which has been made available from the treatment of 146 cases of pulmonary tuberculosis by paravertebral thoracoplasty. This series consists of all patients operated upon by this method at Grasslands Hospital from February, 1932, through July, 1940. A complete follow-up is reported on all but three cases within the past six months. All three not followed were classified as arrested when last heard from.

The procedures used to obtain collapse of pulmonary tissue by surgical means are less than thirty years old. Over these years marked improvement in technique has resulted in a lowering of the mortality rate and an increase in the number of cures. This is especially true during the last ten years in which the most rapid advances have been made. It can be said that certain factors, entering into selection of cases suitable for operation and having to deal with the treatment, are now more or less agreed upon as uniform.

When this work was first undertaken, the selection of cases for thoracoplasty was accomplished by rather conventional requirements, but during the years this has been tempered by experience. In the Tuberculosis Division of Grasslands Hospital, comprising 275 adult beds, the number of cases of advanced disease is high, as in any similar institution, upwards of 90 per cent. In the advanced disease group the basis for operative selection undoubtedly has been broadened, thereby giving certain cases a chance for surgical cure which might otherwise have been considered too far progressed for operation. In the main, we have insisted on adequate previous medical regimen, including minor collapse measures and evidence of productive changes. We have been rather liberal in evaluating contralateral involvement, laryngeal and intestinal disease, and upper age limit as contraindications for operation.

Each patient must have a satisfactory blood count and hemoglobin level and, if necessary, blood transfusions are given to bring these up to normal. We prefer to start the operation at a time when the patient is gaining weight, certainly when there has been no recent serious loss.

For several years we conscientiously carried out vital capacity, circulation time, and venous pressure determinations, believing that a more accurate estimate of the patient's ability to withstand the operative procedure could be arrived at. Vital capacity determinations have been

\*From the Divisions of General Surgery and Tuberculosis, Grasslands Hospital  
Received for publication, Aug. 29, 1941.

more or less in vogue for periods of a few years since about 1850. Its popularity has vacillated but it has been revived, from time to time, by hopeful workers in the field of respiratory diseases, especially with the development of new surgical procedures, in which the test was thought to have prognostic bearing. During the 1920's, when thoracoplasty became a more frequently used operation, the test again sprang into prominence. During the past few years doubt has again arisen as to its real value and its limitations emphasized. This has resulted in more refined methods of functional cardiorespiratory determinations. Many clinics, including our own, are now encouraging more careful studies into functional respiratory reserve for patients considered for thoracoplasty. We are encouraged by the information provided by bronchspirometry and are equipping our clinic with apparatus for detailed studies by Dr. William A. Zavod.

Because of the numerous factors involved in the determination of vital capacity, such as loss or gain in weight, cardiac disease, fluid or air in the chest cavity, the effects of phrenic nerve interruption and emphysema, the accuracy of this test as a guide may be unreliable. Given two patients with similar clinical and x-ray findings, one often finds wide variations in the anticipated respiratory reserve. We still use the test because it does provide some information. We feel that the lower limit of vital capacity should be 40 per cent. However, if after removal of ribs it is thought that there will not be a harmful decrease in the amount of good lung tissue, then we do not hesitate to proceed with a vital capacity of less. But, in general, patients with a reading of less than 40 per cent are apt to do poorly. The test is repeated after each stage of the operation.

In evaluating the results of venous pressure estimations before operation and between stages, we found no great variations in the readings. If it was observed that the venous pressure was high after any given stage, we were inclined to wait a longer interval before proceeding with the next operation, as emphasized by Overholt and Pilcher.<sup>1</sup> During the past two years the test has not been done routinely because the results apparently did not justify its use.

For several years the circulation time was determined. This has also been abandoned as we came to the conclusion that no valuable help was obtained in evaluating the surgical risk. We have depended, to a large extent, on clinical judgment and experience to estimate this part of the patient's share in the prognosis.

In general, the contraindications to operation are advanced contralateral disease, advanced intestinal and renal disease, lack of inherent ability to form fibrosis or inadequate functional reserve.

Generally speaking, patients operated upon by us fall into groups of favorable, doubtful, and poor risks. We have come to the conclusion that the following factors make up the three grades for evaluation of the risk:

# PARAVERTEBRAL THORACOPLASTY FOR THE TREATMENT OF PULMONARY TUBERCULOSIS

## A REPORT OF 146 CASES WITH FOLLOW-UP

GEORGE C. ADIE, M.D., LESTER C. HUESTED, M.D.,  
WILLIAM G. CHILDRESS,\* M.D., AND HORACIO E. PEREZ,\* M.D.,  
VALHALLA, N. Y.

THE object of this paper is to review the material which has been made available from the treatment of 146 cases of pulmonary tuberculosis by paravertebral thoracoplasty. This series consists of all patients operated upon by this method at Grasslands Hospital from February, 1932, through July, 1940. A complete follow-up is reported on all but three cases within the past six months. All three not followed were classified as arrested when last heard from.

The procedures used to obtain collapse of pulmonary tissue by surgical means are less than thirty years old. Over these years marked improvement in technique has resulted in a lowering of the mortality rate and an increase in the number of cures. This is especially true during the last ten years in which the most rapid advances have been made. It can be said that certain factors, entering into selection of cases suitable for operation and having to deal with the treatment, are now more or less agreed upon as uniform.

When this work was first undertaken, the selection of cases for thoracoplasty was accomplished by rather conventional requirements, but during the years this has been tempered by experience. In the Tuberculosis Division of Grasslands Hospital, comprising 275 adult beds, the number of cases of advanced disease is high, as in any similar institution, upwards of 90 per cent. In the advanced disease group the basis for operative selection undoubtedly has been broadened, thereby giving certain cases a chance for surgical cure which might otherwise have been considered too far progressed for operation. In the main, we have insisted on adequate previous medical regimen, including minor collapse measures and evidence of productive changes. We have been rather liberal in evaluating contralateral involvement, laryngeal and intestinal disease, and upper age limit as contraindications for operation.

Each patient must have a satisfactory blood count and hemoglobin level and, if necessary, blood transfusions are given to bring these up to normal. We prefer to start the operation at a time when the patient is gaining weight, certainly when there has been no recent serious loss.

For several years we conscientiously carried out vital capacity, circulation time, and venous pressure determinations, believing that a more accurate estimate of the patient's ability to withstand the operative procedure could be arrived at. Vital capacity determinations have been

\*From the Divisions of General Surgery and Tuberculosis, Grasslands Hospital.  
Received for publication, Aug. 29, 1941.

The role played by phrenic nerve paralysis as an aid in major collapse is, in our experience, a minor one. We formerly used permanent interruption of the nerve for numerous accepted indications which, in the course of time, proved to be of questionable value and hence died a slow but certain death. Temporary nerve paralysis still has a place but its indications have decreased and it is now used by us mainly to control hemorrhage or to give mechanical advantage to pneumothorax. Phrenic exeresis has never been done by us, the procedure being considered too hazardous. We believe that a functioning diaphragm will aid in clearing secretions from the lower lobes and maintain to a certain extent a more adequate function of the air-containing tissue in the uncollapsed portion of the lung.

In this series, preceding thoracoplasty, closed pneumonolysis was done in 23 instances and open pneumonolysis in 1. Extrapleural pneumothorax was done in 5 cases, in 2 instances in preparation for thoracoplasty. In 3 cases the procedure alone proved to be a therapeutic failure. Apicolysis was done in 4 of the series and oleothorax in 4. Pneumoperitonemum has been tried in 6 cases.

Cavity size varied from 2 to 16 cm., the average for the entire group being 5.4 cm. Cavities were located on the right side in 77 and on the left in 69 instances.

Forty-six of the patients receiving thoracoplasty had clear fluid in the pleural space, usually complicating pneumothorax. Twenty-seven had frank tuberculous empyema, 11 of whom had shown a mixed pyogenic infection at one time or another. In 7 of these bronchopleural fistulas were known to be present.

Anesthesia, in the early days, was somewhat of a problem, but never a serious one, because the anesthetic staff at Grasslands Hospital has been uniformly capable during the years. We have passed through the local anesthesia phase, through the avertin gas and oxygen combination, the spinal for lower stages, the evipal plus cyclopropane, and finally adopting the cyclopropane with the intratracheal tube as the most satisfactory, from the patient's as well as the surgeon's standpoint. The position of the patient on the table is such that the head is lower than the chest, the head of the table being turned down about 15 degrees from the horizontal. This allows easy removal of secretions from the trachea through aspiration by the anesthetist or escape from the mouth after gravitation to the pharynx.

Three hundred and twenty-three staged operations were done and 15 patients had, in addition, one or more supplementary operations.

When this series was started in 1932, the operation was frequently done from below up. The complete thoracoplasty was always done in three stages or more. We prefer to wait about four weeks between stages, this period being determined by the patient's reaction and x-ray findings from films made about three or four weeks after any given

## Grade I

- a. Under 40 years of age
- b. Localized disease, stationary lesion
- c. Afebrile
- d. Gaining weight
- e. Adequate functional reserve
- f. Normal blood pressure
- g. Minimal concurrent disease

## Grade II

- a. Upper age group
- b. Stationary or slightly progressive lesion
- c. Contralateral disease which is stationary
- d. Moderate functional reserve
- e. Controlled empyema
- f. Without bronchopleural fistula
- g. Mild concurrent tuberculous disease

## Group III

- a. Upper age limit
- b. Acute lesion of any type
- c. Contralateral progressive disease
- d. Bronchopleural fistula
- e. Hypertension
- f. Extensive concurrent tuberculous disease
- g. Extensive fibrosis and emphysema with low functional reserve.

Alexander<sup>2</sup> has pointed out the disadvantages of such a classification, and on the whole, we agree with him, but when faced with such a large group of advanced cases, where the outlook is not always good, we feel justified in gauging our prognosis with established facts.

In accordance with this classification, we find: favorable, 76; doubtful, 41; poor, 29.

Racial analysis reveals that there were 119 patients of the white race, 1 of the yellow race, and 26 negroes.

Table I shows the series according to age and sex.

TABLE I  
THORACOPLASTIES BY AGE AND SEX

AGE	MALE	FEMALE	TOTAL
11-20 yr.	2	5	7
21-30 yr.	27	31	58
31-40 yr.	30	13	43
41-50 yr.	19	11	30
51-60 yr.	7	1	8
	85	61	146

The average length of treatment prior to operation for the series was about two years. Pneumothorax had proved to be an operative or therapeutic failure in all cases. Phrenic nerve operations were performed on 31 of the patients before thoracoplasty and on 2 after operation.

months and general improvement is in evidence. The patients are then placed on graduated exercise until one hour's walking exercise twice a day or its equivalent is reached and improvement is such that the patient can be discharged as arrested. After discharge the patients are returned to clinic for examination every three months during the first year and thereafter every six months or as indicated. All follow-up examinations include x-ray of the lungs and concentrated sputum examination, in addition to the routine interval history and physical examination. Culture or guinea pig studies are now being done when sputum conversion is reported on concentration.

Of the 146 patients operated upon, 100, or 68.4 per cent, are living and 46, or 31.6 per cent, are dead from all causes. These deaths have occurred in a postoperative period ranging from one to eight years.

Table II gives the analysis of results of thoracoplasty.

TABLE II  
RESULTS OBTAINED IN 146 PATIENTS

Arrested		93 (63.7%)
Living	85	
Dead from other causes than tuberculosis or operation	8	
Improved		7 ( 4.8%)
Unimproved		8 ( 5.4%)
Dead		46 (31.5%)
Operative	12 ( 8.2%)	
Progressive disease	25 (17.1%)	
Other causes	9 ( 6.2%)	

An analysis of the deaths according to age and sex is shown in Table III.

TABLE III  
DEATHS ACCORDING TO AGE AND SEX

AGE	MALE	FEMALE	TOTAL	NO. OF OPERATIONS
11-20 yr.	0	2	2	5
21-30 yr.	7	8	15	56
31-40 yr.	9	3	12	41
41-50 yr.	10	1	11	31
51-60 yr.	3	0	3	10
	29	17	46	143

Table IV gives the results by selective groups:

TABLE IV  
DEATHS ACCORDING TO RISK  
(ALL CAUSES, ONE TO EIGHT YEARS)

Favorable		76
Dead	3 ( 3.9%)	
Doubtful		41
Dead	20 (48.8%)	
Poor		29
Dead	23 (79.3%)	

The observations made on this group of patients are especially valuable, in our opinion, because of the almost complete follow-up. Only

stage. In 3 instances, an unusually long time between stages elapsed because of contralateral spread, hemorrhage, and unfavorable postoperative recovery.

The first partial thoracoplasty in this series was done in 1932 in two stages, and since 1934 the two-stage six or seven rib thoracoplasty from above down has predominated. The complete operation has been done only eighteen times in the past four years.

In 1936 we began to use extrafascial apicectomy as recommended by Semb.<sup>3</sup> Since then it has been used in every case where indicated. It is our feeling that more cavity closures have been obtained by use of this adjunct. The cavities, instead of being compressed from above down against the mediastinum, appear to change their shape before closure as though the pressure were being applied from behind, laterally and above. Mobilization of the apex, especially in the posterior gutter, allows the lobe to be pushed more anteriorly. This procedure lengthens the time of operation ten to twenty minutes, and requires a careful dissection to avoid injury to the nerves and the subclavian vein. We have had no injury to the subclavian vein, one minor injury to the ulnar division of the brachial plexus, as evidenced by pain for three months in the forearm and hand, and one case of sympathetic nerve disturbance. In several patients, directly after apicectomy, we have observed a rise in temperature to 102 or 103°, symptoms of toxicity, and a decrease in expectoration. We have regarded this as caused by an obstruction to drainage of the cavity. This state persists for a few days and promptly subsides when the contents of the obstructed cavity are evacuated. We do not feel that the ultimate closure of the cavity is affected by this episode.

The complications encountered soon after operation were, in the main, spread of the disease locally or in the contralateral lung, pulmonary hemorrhage, severe dyspnea, and cardiac embarrassment. We have not seen a single case of meningitis or brain abscess as a complication. One patient developed a popliteal embolus which required subsequent amputation of the leg. Infection of the wound in this group of approximately 300 operations occurred as follows: 8 massive, 5 moderate, and 10 mild. In 4 cases chronic discharging sinuses persisted. All the infections were eventually controlled and no death was attributable to wound infection.

The late complications were chiefly progressive disease, reopening of bronchopleural fistulas, and in one case, development of a bronchopleural cutaneous fistula. Osteomyelitis of the ribs has occurred infrequently and has not persisted as a complicating factor.

There is less cervical spinal deformity if the transverse processes of the first three vertebrae are left long.

After surgery we prefer to keep the patients on strict bed rest until the sputum has been repeatedly negative for a period of three to six

months and general improvement is in evidence. The patients are then placed on graduated exercise until one hour's walking exercise twice a day or its equivalent is reached and improvement is such that the patient can be discharged as arrested. After discharge the patients are returned to clinic for examination every three months during the first year and thereafter every six months or as indicated. All follow-up examinations include x-ray of the lungs and concentrated sputum examination, in addition to the routine interval history and physical examination. Culture or guinea pig studies are now being done when sputum conversion is reported on concentration.

Of the 146 patients operated upon, 100, or 68.4 per cent, are living and 46, or 31.6 per cent, are dead from all causes. These deaths have occurred in a postoperative period ranging from one to eight years.

Table II gives the analysis of results of thoracoplasty.

TABLE II  
RESULTS OBTAINED IN 146 PATIENTS

Arrested		93 (63.7%)
Living	85	
Dead from other causes than tuberculosis or operation	8	
Improved		7 (4.8%)
Unimproved		8 (5.4%)
Dead		46 (31.5%)
Operative	12 (8.2%)	
Progressive disease	25 (17.1%)	
Other causes	9 (6.2%)	

An analysis of the deaths according to age and sex is shown in Table III.

TABLE III  
DEATHS ACCORDING TO AGE AND SEX

AGE	MALE	FEMALE	TOTAL	NO. OF OPERATIONS
11-20 yr.	0	2	2	5
21-30 yr.	7	8	15	56
31-40 yr.	9	3	12	41
41-50 yr.	10	4	14	31
51-60 yr.	3	0	3	10
	29	17	46	143

Table IV gives the results by selective groups:

TABLE IV  
DEATHS ACCORDING TO RISK  
(ALL CAUSES, ONE TO EIGHT YEARS)

Favorable		76
Dead	3 (3.9%)	
Doubtful		41
Dead	20 (48.8%)	
Poor		29
Dead	23 (79.3%)	

The observations made on this group of patients are especially valuable, in our opinion, because of the almost complete follow-up. Only



stage. In 3 instances, an unusually long time between stages elapsed because of contralateral spread, hemorrhage, and unfavorable postoperative recovery.

The first partial thoracoplasty in this series was done in 1932 in two stages, and since 1934 the two-stage six or seven rib thoracoplasty from above down has predominated. The complete operation has been done only eighteen times in the past four years.

In 1936 we began to use extrafascial apicolysis as recommended by Semb.<sup>3</sup> Since then it has been used in every case where indicated. It is our feeling that more cavity closures have been obtained by use of this adjunct. The cavities, instead of being compressed from above down against the mediastinum, appear to change their shape before closure as though the pressure were being applied from behind, laterally and above. Mobilization of the apex, especially in the posterior gutter, allows the lobe to be pushed more anteriorly. This procedure lengthens the time of operation ten to twenty minutes, and requires a careful dissection to avoid injury to the nerves and the subclavian vein. We have had no injury to the subclavian vein, one minor injury to the ulnar division of the brachial plexus, as evidenced by pain for three months in the forearm and hand, and one case of sympathetic nerve disturbance. In several patients, directly after apicolysis, we have observed a rise in temperature to 102 or 103°, symptoms of toxicity, and a decrease in expectoration. We have regarded this as caused by an obstruction to drainage of the cavity. This state persists for a few days and promptly subsides when the contents of the obstructed cavity are evacuated. We do not feel that the ultimate closure of the cavity is affected by this episode.

The complications encountered soon after operation were, in the main, spread of the disease locally or in the contralateral lung, pulmonary hemorrhage, severe dyspnea, and cardiac embarrassment. We have not seen a single case of meningitis or brain abscess as a complication. One patient developed a popliteal embolus which required subsequent amputation of the leg. Infection of the wound in this group of approximately 300 operations occurred as follows: 8 massive, 5 moderate, and 10 mild. In 4 cases chronic discharging sinuses persisted. All the infections were eventually controlled and no death was attributable to wound infection.

The late complications were chiefly progressive disease, reopening of bronchopleural fistulas, and in one case, development of a bronchopleural cutaneous fistula. Osteomyelitis of the ribs has occurred infrequently and has not persisted as a complicating factor.

There is less cervical spinal deformity if the transverse processes of the first three vertebrae are left long.

After surgery we prefer to keep the patients on strict bed rest until the sputum has been repeatedly negative for a period of three to six

Nine of the cases originally presented caseous pneumonic lesions where pneumothorax had been attempted and abandoned because of failure. Seven were in negroes, and two in whites, all complicated by empyema and 3 having proved bronchopleural fistulas. In another case, the sputum had been negative for eight years, but thin bloody fluid continued to build up beneath the thoracoplasty, necessitating repeated aspirations. A bronchopleural fistula suddenly developed and the fluid became secondarily infected necessitating open drainage. The patient died in seven months from spread of the tuberculous disease. Another patient died of extensive amyloidosis five years after a negative sputum. On post-mortem examination no active tuberculosis was found and a healed cavity was described, but there was a large loculated empyema pocket in the posterior gutter, filled with thick tuberculous pus. The other 13 patients died of progressive tuberculosis and in all instances the contralateral lung was extensively involved.

It is interesting to note that healing of cavity was described in 3 of the post-mortem examinations.

All of our patients were classified as far advanced. Most of these were chronic cases previously receiving long sanatorium treatment without improvement and in whom treatment would have been prolonged. This is illustrated in the case of a patient who had received nine years of sanatorium treatment and who was discharged one year and four months after surgery was completed.

All patients classified as arrested and who have been followed in our clinic are in excellent condition. There is some degree of scoliosis present in all patients graded by us as severe in 8, moderate in 10, and slight in the others, but is not incapacitating in any instance. The majority of these arrested cases are employed in some gainful occupation. As regards function, meaning good arm motion and adequate vital capacity, there are 88 good, 11 fair, and 1 poor result. Deformity from a purely aesthetic point of view revealed 89 good, 14 fair, and 6 poor.

Our results show that 68.5 per cent of our patients were improved and of this group 63.7 per cent were classified as arrested, or apparently cured, after being subjected to rigid examination. These figures compare favorably with those of Freedlander and Wolpaw,<sup>4</sup> who reported 57 per cent negative sputum cases and 9 per cent improved, or a total of 66 per cent improved out of a series of 85 cases. They also compare favorably with those of Overholt,<sup>5</sup> Maurer and de Savitseh,<sup>6</sup> and Coryllos<sup>7</sup> all of whom report approximately 70 per cent of the operated cases improved but do not, however, mention the number of cases in which there has been permanent sputum conversion. Wangenstein, Carlson, and Bowers,<sup>8</sup> in a series of 42 cases, reported 50 per cent with negative sputum and a total of 71.5 per cent improved. Our figures show definite improvement over those collected from the literature by Dolley, Jones, and Paxton,<sup>9</sup> representing a total of 636 cases

3 patients have not been heard from during the last six months and all of these were classified as arrested when last reported. Of the remaining patients, all but 22 were examined by us. The others responded to questionnaire.

The 9 deaths due to causes other than tuberculosis were: suicide (1); this patient was depressed because we were unable to proceed with the second stage, due to spread of the disease; nontuberculous nephritis (1), three years after closed cavity and negative sputum; involutional melancholia (1), six months after negative sputum; nontuberculous pneumonia (1), one year after negative sputum; lymphosarcoma (1), two years after a successful result. One death occurred in a white male, aged 44 years, with arrested disease for two years, who suddenly developed weakness in the lower extremities, with loss of sphincter control of the urinary bladder. A clinical diagnosis of transverse myelitis was made. He failed rapidly and expired seven days later. An autopsy revealed healed pulmonary tuberculosis. There was considerable emphysema and arteriosclerosis and a liver weighing 1,575 Grams, which revealed a hematoma 1 cm. in diameter and extending to about  $\frac{3}{4}$  to 1 cm. below the capsule. No other cause of death was stated. Two patients died of cardiac decompensation (post mortem on both), one five years after the disease was arrested and the other two years. The other patient was seen in the psychiatric division of this hospital only a few weeks before death and his tuberculosis was arrested at that time. The patient was released from the hospital with a diagnosis of paranoid schizophrenia and died shortly afterward at home.

Twelve deaths (8.2 per cent) occurred within the first ten days after operation. These have been classified as operative deaths, but it is highly questionable if operation alone was responsible. In 3 of these cases, the patients died of massive pulmonary hemorrhage, 1 following the first stage and 2 following the second stage. Five deaths in this group occurred in patients who, from general and x-ray appearance seemed at the time to be good risks, although because of low vital capacity, fall into the doubtful group. All had chronic disease with emphysema and 4 had a vital capacity of less than 40 per cent. Post-mortem examination was obtained in 2 of these 5 patients and no other cause of death could be found. They all had dyspnea and cyanosis following operation. One of the 12 died of acute cardiac dilatation, proved by post-mortem examination. The other 3 deaths in this group were attributed to postoperative shock.

Twenty-five of the deaths were due to progressive pulmonary and pleural disease. One of these patients was considered an arrested case but was readmitted two years later with recurrent pulmonary hemorrhage, from which he eventually died, although the sputum was negative and at post-mortem examination the original cavity was described as healed. However, there was extensive bronchiectasis beneath the thoracoplasty, giving rise to hemorrhage.

# THE SURGICAL TREATMENT OF LARGE CARBUNCLES IN DIABETIC AND NONDIABETIC INDIVIDUALS

WITH A REPORT OF TWENTY CASES

CHARLES W. McLAUGHLIN, JR., M.D., OMAHA, NEB.

(From the Department of Surgery, University of Nebraska College of Medicine)

FEW lesions are encountered more frequently in surgical practice than are ordinary furuncles. Excepting those developing on the face, they attract little attention from the surgeon. The vast majority of these minor infections respond to a wide variety of therapeutic measures, resulting eventually in complete cure. The fact that furuncles rank high among the causes of disability in industry, producing their full share of pain to the unfortunate patient, is all too frequently overlooked.

In contrast to these simple infections, a true carbuncle with extensive involvement of the subcutaneous tissue and multiple draining sinuses through the overlying skin presents a surgical problem of major importance. The seriousness of these lesions is further increased since they so frequently develop in older individuals with diabetes, nephritis, or other debilitating disease.

During the past few years we have observed a series of twenty patients with carbuncles of major size, necessitating hospitalization for treatment. For the purpose of this study all cases have been excluded which presented with small carbuncles suitable for treatment in the outpatient department or in office practice.

Several methods of treatment were used in the management of these twenty patients and this is quite in keeping with the highly divergent opinions expressed in the surgical literature. An analysis of our cases was therefore undertaken, together with a review of the experience of others, to more critically evaluate the therapeutic results obtained in the treatment of these lesions.

## REPORT OF CASES

In any series of cases of large carbuncles it is essential that those developing in nondiabetic patients be considered apart from those in diabetics. The fulminating character of the diabetic carbuncle with its high attendant mortality presents a surgical problem of major importance and demands that this group of patients be considered separately.

### (a) Carbuncles in nondiabetic patients.

There were thirteen patients in this group, of whom eight were females and five males. The average age was forty-five years. The most common site was the neck and shoulders, followed in order by the face, buttocks, and thighs. The average duration of the lesion on admission was thirteen days, the longest period being six weeks and the shortest two

Received for publication, Aug. 6, 1941.

with only 43 per cent improved. No doubt this is due to improvement in selection and technique.

Of our improved group, all are able to do part- or full-time work but are handicapped by recurrent positive sputum or slight pulmonary changes evidenced by x-ray and elevation of temperature and malaise from time to time.

We believe that poor results from thoracoplasty can be expected in chronic cases with emphysema and fibrosis, where there is limited functional reserve. Better selection in this group can be made by careful respiratory functional determinations before operation as described by Richards and Cournand.<sup>10</sup> Especially hazardous, in our limited experience, are the acute lesions temporarily controlled with pneumothorax, when complicated by empyema and particularly if bronchopleural fistulas are present.

Undoubtedly other complications, such as systemic disease, extent of involvement, protracted multiform tuberculosis, and age influence results, but these are not factors of special interest in this series.

#### SUMMARY

1. One hundred forty-six cases of paravertebral thoracoplasty for the treatment of pulmonary tuberculosis are reported.
2. Complete follow-up was obtained on all but 3 patients, who were classified as arrested when last heard from.
3. Improvement occurred in 68.5 per cent and of these 93 or 63.7 per cent, by critical analysis were arrested or apparently cured.
4. Forty-six, or 31.5 per cent, of the patients are dead from all causes during one to eight years. Twelve, or 8.2 per cent, are listed as operative deaths; 9, or 6.2 per cent, died of causes other than tuberculosis; and the remaining 25, or 17.1 per cent, died of progressive tuberculous disease.

#### REFERENCES

1. Overholt, R. H., and Pileher, L. S., Jr.: Changes in Venous Pressure After Thoracoplasty—Its Significance in Relation to Extent of Rib Removal, *J. Thoracic Surg.* 4: 269, 1935.
2. Alexander, John: The Collapse Therapy of Pulmonary Tuberculosis, Springfield, Ill., 1937, Charles C Thomas, Publisher.
3. Semb, C.: Thoracoplasty With Extrafascial Apicolysis, *Brit. M. J.* 2: 650-656, 1937.
4. Freedlander, S. O., and Wolpaw, S. E.: Control Group for Studying End Results of Thoracoplasty, *J. Thoracic Surg.* 6: 477-490, 1937.
5. Overholt, R. H.: Selective Thoracoplasty With Lung Mobilization, *Am. Rev. Tuberc.* 37: 152-173, 1938.
6. Maurer, A., and de Sivitsch, E.: Thoracoplasty in Treatment of Pulmonary Tuberculosis, *Am. Rev. Tuberc.* 38: 738-745, 1938.
7. Coryllos, Pol N.: Surgery of Pulmonary Tuberculosis, *Quart. Bull., Sea View Hosp.* 1: 456-475, 1936.
8. Wangensteen, O. H., Carlson, H. A., and Bowers, W. P.: Partial Thoracoplasty for Pulmonary Tuberculosis, *J. Thoracic Surg.* 7: 265-281, 1938.
9. Dolley, Frank S., Jones, John C., and Paxton, John R.: Late Results of Thoracoplasty, *Am. Rev. Tuberc.* 39: 145-161, 1939.
10. Richards, D. W., Jr., and Cournand, A.: Pulmonary Function in Pulmonary Tuberculosis Under Various Forms of Collapse Therapy, *Nat. Tuberc. A. Tr.* 35: 87-104, 1939.

days. In size these carbuncles varied from 3 to 20 cm. in diameter, the smaller lesions being those on the lips and face, while the very extensive ones were those on the neck and shoulders. The therapy employed is tabulated in Table I.

Carbuncles on the face were treated entirely by conservative measures which included bed rest, continuous moist borie applications, and x-ray therapy in certain instances. Incision was employed in these cases only when it became necessary to drain a well-localized abscess.

Carbuncles appearing in other areas than the face were all treated by cruciate incision with underentting of the skin flaps. In two very extensive cases x-ray was used in conjunction with wide incision as a pre- and postoperative adjunct. It was necessary to operate on one patient a second time because of further local extension of the infection. The average period of hospitalization for the group was nineteen days. Skin grafts were necessary in two cases but the remaining wounds healed without grafting in an average period of six weeks. There was only one death in this group of patients, resulting from septicemia and endocarditis. This man, aged sixty-seven years, with a very extensive carbuncle of his neck, made a good surgical recovery after cruciate incision and the subsequent application of split grafts. He was dismissed from the hospital with his wound almost healed. Two months later he was readmitted after an illness of two weeks. He was found to have a *Staphylococcus aureus* septicemia and post-mortem examination disclosed an acute vegetative endocarditis. There seems little doubt that this man's fatal illness resulted from a late complication of the original carbuncle.

(b) *Carbuncles in diabetic patients.*

This group of seven patients averaged fifty-six years of age and six occurred in males (Table II). Two of the seven were unaware that they had diabetes prior to admission while the remaining five were known diabetics for periods ranging from six months to thirty years. None of this latter group of known diabetics had been under proper medical management before the onset of their present illness. Six of the seven were definitely overweight, averaging 182 pounds.

These seven patients were all acutely ill on admission, with marked pain, fever, and prostration. A leucocytosis was present in every instance, averaging 20,000 cells per cubic millimeter for the group. In those cases in which blood smears were made, there was a striking shift to the left in the polymorphonuclear series, the stab cell counts averaging 22 per cent. These seven patients with diabetes responded in the usual manner when infection became established. In every case the diabetes became uncontrolled in spite of large and increasing insulin dosage, adequate drainage being the only means of bringing the altered metabolism into abeyance. One of these patients was treated entirely

TABLE I  
CARBUNCLES IN NONDIABETIC PATIENTS

CASE	SEX	AGE	SIZE	SITE DURATION	TREATMENT				RESULT		HOS- PITAL DAYS	COMMENT
					CON- SERVA- TIVE	X-RAY	X-RAY SURGERY	SURGERY	RECOV- ERED	DIED		
1	F	25	4 cm.	Buttocks 6 days				Cruciate	Yes		2	Healed 2 wk.
2	F	63	15 cm.	Back 3 wk.				Cruciate	Yes		38	Skin graft; healed 8 wk.
3	F	41	9 cm.	Buttocks 1 wk.				Cruciate	Yes		7	Healed 6 wk.
4	F	15	18 cm.	Neck 2 wk.				Cruciate	Yes		28	Skin graft; healed 6 wk.
5	F	76	4 cm.	Back 2 wk.				Cruciate	Yes		8	Grafts not necessary
6	F	20	3 cm.	Hand 2 days				Cruciate	Yes		4	Healed 2 wk.
7	M	74	10 by 8 cm.	Shoulder 6 wk.			X Cruciate		Yes		32	Mental changes; x-ray not given thor- ough trial
8	M	67	20 by 20 cm.	Neck 4 wk.			X Cruciate			Yes	70	Patient dismissed improved; fatal en- doocarditis 2 mo.
9	M	34	8 cm.	Thigh 1 wk.				Cruciate	Yes		10	Practically healed on dismissal
10	M	60	11 by 7 cm.	Neck 4 wk.				Cruciate 2 x	Yes		30	Two operations done; healed 7 wk.
11	F	25	3.5 cm.	Lip 3 days	X				Yes		7	Spontaneous drainage with x-ray and hot packs
12	F	40	3 cm.	Nose 3 days	X				Yes		5	Spontaneous drainage with hot packs
13	M	18	3 cm.	Lip 4 days	X				Yes		8	Spontaneous drainage with x-ray and hot packs

by conservative means, one by cruciate incision alone, and the remaining five by x-ray therapy, and surgical drainage. Surgical excision was carried out in one of these five patients, cruciate incision being employed in the other four. Extension of the inflammatory process necessitated secondary operations in two patients (Table III). Sulfathiazole

TABLE III  
DIABETIC PATIENTS WITH MAJOR CARBUNCLES  
TREATMENT AND RESULTS

CASE	TREATMENT				RESULTS		HOSPITAL DAYS	CAUSE OF DEATH	COMMENT
	X-RAY	X-RAY AND SURGERY	SURGERY ALONE	CONSERVATIVE	RECOVERED	DIED			
1		Yes Incision			Yes		21		Opened when well localized
2				Yes	Yes		36		Spontaneous drainage
3			Cruciate			Yes	4	Septicemia	Uncontrolled diabetic; no response to therapy; sepsis and pyemia
4		Yes Cruciate			Yes		46		X-ray for 6 days; diabetes not controlled; lesion unchanged; response to surgery
5		Yes Cruciate 2 operations				Yes	31	No post mortem	Terminal leucopenia; possibly sulfathiazole effect
6		Yes Cruciate			Yes		66		X-ray 9 days; lesion unchanged; diabetes not controlled; response to surgery
7		Yes, 3 operations X-ray Transfusion				Yes	32	Sepsis	Severe diabetic; no previous control; surgery too conservative at outset; no resistance

in large doses was used as an adjunct to x-ray and surgery in two patients, transfusion also being employed in the same individuals.

There were three deaths in this small series of diabetic patients, resulting in a mortality of 42.8 per cent for the group.

CASE 1.—An obese male, 72 years of age, was acutely ill on admission to the University Hospital, with a temperature of 101° F. A carbuncle of the neck, 12 × 6 cm. in diameter, had been present for seventeen days. Diabetes was discovered on admission to hospital. Treatment consisted of wide cruciate incision together with diabetic care. The diabetes remained uncontrolled and the patient made no response to treatment. Death occurred from septicemia four days after admission. A nonhemolytic streptococcus was demonstrated on blood culture. No post-mortem permitted.



TABLE II  
DIABETIC PATIENTS WITH MAJOR CARBUNCLES  
CLINICAL DATA

CASE	SEX	AGE WEIGHT	KNOWN DIABETIC	SITE LESION	SIZE	DURATION	TEMPERATURE ADMISSION	W. B. C.	DAILY INSULIN	ORGANISM
1	M	62 200	Yes 30 yr.	Nose	3 cm.	3 days	101°	16,000	60 units not con- trolled	<i>Staph. aureus</i>
2	M	34 107	Yes 6 mo.	Cheek	3 cm.	10 days	99.4°	6,700 19% stab cells	60 units not con- trolled	Nonhemolytic <i>streptococcus</i>
3	M	72 165	Yes 5 days	Neck	12 by 6 cm.	17 days	101°	12,600 48% stab cells	60 units not con- trolled	Nonhemolytic <i>streptococcus</i>
4	M	64 194	Yes 3 yr.	Neck	8 by 10 cm.	10 days	100°	16,200 2% stab cells	60 units not con- trolled	<i>Staph. aureus</i>
5	M	44 204	Yes 5 days	Neck	16 by 18 cm.	2 wk.	101.4°	30,800 36% stab cells	200 units not con- trolled	Hemolytic <i>Staph. aureus</i>
6	F	57 160	Yes 17 yr.	Neck	6 by 8 cm.	3 wk.	101°	32,000 24% stab cells	90 units not con- trolled	<i>Staph. aureus</i>
7	M	63 180	Yes 10 mo.	Neck	12 by 12 cm.	10 days	100.8°	26,100 5% stab cells	75 units not con- trolled	Not cultured

when therapy is started early. Surgical drainage becomes necessary to control the lesion in approximately 33 per cent of any group of patients receiving initial x-ray therapy. Hodges,<sup>5</sup> King,<sup>3</sup> Andrews,<sup>6</sup> and Light and Sosman,<sup>1</sup> all agree that the highest percentage of failures with x-ray therapy occurs in the treatment of deep carbuncles of the neck, and these authors all favor surgical incision for this type of lesion. In carbuncles of the blush area of the face x-ray therapy is now almost uniformly employed with an appreciable reduction in the mortality.

TABLE IV  
X-RAY THERAPY IN THE TREATMENT OF MAJOR CARBUNCLES

AUTHOR	TOTAL NO. CASES	CASES X-RAY THERAPY ONLY	CASES AIDED %	CASES CURED %	CASES X-RAY FAILURE	CASES X-RAY FAILURE %	CASES X-RAY AND SURGERY	MORTALITY		COMMENT
								CASES	%	
Light and Sosman	50	34	66	60	16	32	16 33%	2	4	Failure in 40% lesions neck in men
Fior	56	38	70	60	1	1	18 33%	0	0	
King	39	36	70	66	3	33	3 8.3%	0	0	Surgery better for deep lesions of neck
Lewis	16	14		87.4	2	12.4	2 12.4%	0	0	
Hodges	26	24		92	2	8	2 8%	0	0	Advise surgery for deep neck lesions in men

(b) *X-ray therapy in conjunction with surgical drainage* is the most popular method of treatment employed today in the treatment of major carbuncles. In Table V several reported series of cases are summarized indicating the methods of therapy and results obtained by different surgeons. One may conclude that x-ray therapy is definitely worthy of a trial in the treatment of nondiabetic carbuncles, excepting those deep lesions on the neck. If evidence of improvement is not apparent after five days' therapy, radical surgical drainage is indicated.

In analyzing these cases one outstanding fact is apparent. Most nondiabetic patients with major carbuncles recover unless the individual develops a septicemia with multiple abscesses or an endocarditis. The mortality in the nondiabetic group averages approximately 3 per cent. In contrast, the diabetic patient with a major carbuncle has a very different prognosis. Our experience, which is supported by the observations of others, has led us to consider such a lesion as serious as a moist gangrenous limb in a diabetic patient. With the onset of infection, the carbohydrate metabolism invariably becomes refractory to medical therapy, and fails to respond with the employment of conservative surgical measures. The mortality in this group of patients ranges from 25 to 40 per cent in the reported series. These patients are usually

CASE 2.—An obese male, 44 years of age, was admitted to the University Hospital acutely ill with a temperature of  $101.4^{\circ}$  F. An extensive carbuncle of the neck, measuring  $16 \times 18$  cm., had been present for two weeks. Diabetes was discovered for the first time five days prior to admission. Treatment consisted of wide cruciate incision and the incision was enlarged on two occasions because of extension of the lesion. X-ray therapy and large doses of sulfathiazole were also employed. The diabetes, which was at first uncontrollable in spite of 200 units of insulin per day, became regulated when adequate surgical drainage was obtained. Recovery seemed assured and the wound was healing satisfactorily when the patient suddenly became listless, apathetic, and irrational. A leucopenia developed with complete agranulocytosis. Death occurred on the thirty-first hospital day, ninety hours after the onset of this complication. A blood culture on the last day of life was negative. A post-mortem was not permitted. The clinical impression was that death probably resulted from agranulocytosis incident to sulfathiazole.

CASE 3.—An obese male, 64 years of age, was admitted to the Methodist Hospital with a temperature of  $100.8^{\circ}$  F. A carbuncle of the neck,  $12 \times 12$  cm., had been present for a period of ten days. The patient was a known diabetic of ten months' duration but had not been under adequate medical control. Cruciate incision, without undercutting, was carried out on two occasions but in neither instance was the entire area widely opened. Sulfathiazole was given in large doses, x-ray therapy was given daily, and the patient received two transfusions. The inflammatory process continued to advance, sepsis became more marked, and the diabetes was uncontrolled on 75 units of insulin per day. The patient was seen in consultation and more adequate surgical drainage was advised. Wide cruciate incision with complete undercutting of the flaps was carried out under pentothal sodium anesthesia. Temporary improvement was noted but pulmonary signs developed and death occurred on the thirty-second hospital day. No post-mortem was permitted. It would appear that the initial treatment in this case was too conservative with resultant loss of strength and resistance. It seems possible that more adequate surgical drainage at an earlier date might have altered the ultimate result.

#### DISCUSSION

The principal methods of treatment employed in the treatment of major carbuncles may be considered under four headings.

1. Conservative measures in which rest, hot packs, and x-ray therapy are the principal therapeutic agents.

2. X-ray therapy in conjunction with surgical drainage.

3. Early radical surgical drainage.

4. Miscellaneous methods.

(a) *X-ray therapy.* In Table IV several series of reported cases are summarized in which x-ray therapy was the principal method of treatment. Improved technique of radiation has resulted in providing a very valuable therapeutic agent with the principal advantages of prompt reduction in pain and a very satisfactory cosmetic result. Except in those cases in which treatment is begun very early, the period required for control of these lesions with x-ray is similar or only slightly less than that observed when surgery is employed. In the reported series of cases x-ray therapy alone has been adequate to effect a cure in from 60 to 90 per cent of the patients so treated, the percentage being higher

double cruciate incision with sliding flaps, and Maes<sup>18</sup> a gridiron incision to provide drainage comparable to that produced by the usual cruciate incision with more rapid healing and a smaller scar. We have routinely employed a wide cruciate incision with undercutting of the skin flaps when surgical drainage was undertaken (Fig. 1). Zinc peroxide (Z.P.O.) is a very useful initial dressing for these wounds, followed in a few days by Dakin's solution to facilitate separation of adherent necrotic tissue. The skin flaps are approximated with flamed adhesive tape as soon as the base of the wound is covered with healthy granulation tissue. The resultant scar is usually much less noticeable than anticipated and skin grafts are only occasionally necessary (Fig. 2).



Fig. 1—A, Large carbuncle on back of neck in a diabetic patient of two weeks' duration. B, Appearance ten days after wide cruciate incision with undercutting of skin flaps. Healing was facilitated by approximating the skin flaps with flamed adhesive tape.

It must be constantly borne in mind that the inflammatory process may extend after the primary operation is carried out, necessitating further surgery. We have found this necessary on three occasions in our series of cases.

Practically all now agree that radical surgical methods have no place in the treatment of carbuncles of the upper lip and bluish areas. Lillenthal<sup>19</sup> has recently suggested incision through the vermilion border of the upper lip for the treatment of carbuncles in this region but stresses

obese, often are unaware they have diabetes until their admission to the hospital, and frequently are hospitalized for treatment days or weeks after the development of the carbuncle. We agree with McKittrick and Root<sup>12</sup> that the logical method of treatment demands immediate control of the patient's ketosis and the prompt institution of adequate surgical drainage, providing the lesion is not on the face. Needless delay spent in futile attempts to control the patient's diabetes and limit the inflammatory process by conservative methods results in a lowering of resistance and higher mortality.

TABLE V  
TREATMENT OF MAJOR CARBUNCLES  
SUMMARY OF SEVERAL REPORTED SERIES

		MITCH- NER	O'BRIEN	BER- MAN	FALLIS AND HOOKER	CARP	MC KIT- TRICK AND ROOT	MC- LAUGH- LIN
Total cases		240	130	125	166	153	19	20
Diabetic cases		10	16	21	20	30	19	7
% cases diabetic		2.4%	12.3%	16.8%	12%	19.6%	100%	35%
Therapy non- diabetic patients	Conservative	114		25	36	33		3
	X-ray only		60		13	22		
	X-ray and sur- gery		70		3			2
	Surgery			32	84	56		7
	Incision only	40		67	23			1
	Excision Cases	86		3	4	3		1
Deaths %		3.5%	0.8%	2.0%	2.7%	2.5%		7.6%
Therapy patients with diabetes	Conservative	1				1		1
	X-ray only					6		
	X-ray and sur- gery							4
	Surgery					23	19	2
	Incision only	4						
	Excision Cases	5		6	5	8	5	3
Deaths %		40%	25%	28.5%	25%	27%	26.3%	42.8%
Lesions Face	Cases	83	57		25			4
	Deaths	7	0		5			0
	% Deaths	8.4%	0%		20%			0%

(c) *Radical surgical drainage* is the method of choice when a decision has been made to employ surgery. One has only to recall the characteristic pathology of a carbuncle to realize the futility of obtaining adequate drainage by means of conservative or "medical" incisions. Complete excision of the lesion either with the actual cautery as advocated by Mowery<sup>13</sup> or the electric knife suggested by Jopson<sup>14</sup> has its adherents. Hosford<sup>15</sup> favors this method when feasible in all diabetic patients. These methods undoubtedly do remove the entire infected area but the resultant period of disability and scarring have not contributed to their popularity. Wide cruciate incisions extending completely across the entire area with complete undercutting of the flaps as practiced by Kanavel<sup>16</sup> is probably the most popular method of surgical drainage employed. More recently Livingston<sup>17</sup> has described a

TABLE VI  
THERAPY OF CARBUNCLES  
MISCELLANEOUS METHODS

AUTHOR	CASES	DIA THERMY CAUTERY PUNCTURE	MAG NESIUM SULFATE PASTE	AUTO HEMO INJECTIONS	SUPPURY AND SULFONA MIDES	REFCON FREQ	DIFD	MOR TALITY
Tellman	3	3				3	0	0%
Beling and Abel	13				13	13	0	0%
Morrison	28		28			28	0	0%
Carp	12			12		12	0	0%
Dutt	8			8		8	0	0%
Brown	2			2		2	0	0%

We have had no personal experience with this method but through the courtesy of Dr. Alfred Brown the following two cases are reported in which it was successfully employed.

CASE 1—Male, aged 38 years, was seen on June 9, 1927, with a large furuncle on the back of the neck, present for one week. Hot packs were applied but the following day the lesion was more extensive, having all the characteristics of a true carbuncle. The temperature was 99.4° F, the white blood count 17,400, urine negative. On June 17, 1927, 40 c.c. of whole blood were injected into four quadrants about and beneath the lesion. The following day pain was lessened considerably and there was no evidence of extension. The center of the lesion became soft and there was profuse purulent drainage. Following the initial autohemo injection no further treatment was necessary excepting frequent dressings. Healing progressed rapidly and the patient was dismissed with the wound healed eighteen days after the autohemo injection.

CASE 2—Male, aged 39 years, was seen on November 15, 1928, with typical carbuncle on back of the neck present for period of four days. Urine negative. The patient was immediately admitted to the Clarkson Hospital where the entire periphery of the lesion was injected with autogenous whole blood under gas anesthesia. Pain was promptly relieved and the following day he left the hospital. The inflammatory area rapidly decreased in size and discharge from the center of the area diminished. The patient was dismissed five days after the autohemo injection. Dressings were no longer necessary and healing was complete.

NOTE: We wish to express our appreciation to Dr. Alfred Brown for the privilege of including in this report his two cases successfully treated by autohemo therapy.

#### SUMMARY AND CONCLUSIONS

1. A series of twenty major carbuncles are reported, thirteen developing in nondiabetic and seven in diabetic patients.
2. The mortality in the nondiabetic patients should be low, death almost always resulting from septicemia with its attendant complications.
3. The mortality from large carbuncles developing in diabetic patients is high, ranging from 25 to 42 per cent in the reported series of cases.
4. Conservative measures, including x-ray therapy, should be employed in the treatment of all carbuncles on the face in both diabetic and nondiabetic patients. Ligation of the angular vein in these individuals is not warranted.

the danger of going through infected tissue. It is generally considered that surgical procedures in these regions should be limited to the removal of crusts or simple incision when necessary to release pus from well-localized and completely liquefied pockets. Ligation of the angular vein was advocated by Bailey,<sup>20</sup> in 1928, to prevent the development of cavernous sinus thrombosis, although it was admitted that this only represented one route of drainage from the blush area. More recently Batson<sup>21</sup> has demonstrated by injection experiments that ligation of the angular vein does not prevent septic emboli in the facial vein from



Fig. 2—Late appearance of a very extensive carbuncle of the neck in a nondiabetic patient with destruction of skin through necrosis. Entire area subsequently covered with split grafts.

entering the cavernous sinus by several other routes. Fraser,<sup>22</sup> Gordon,<sup>23</sup> and Roberts,<sup>24</sup> have all pointed out the futility of this procedure and it is rarely employed today.

(d) A group of the less frequently employed methods used in the treatment of carbuncles are listed in Table VI. Of these, autohemotherapy as employed by Carp<sup>25</sup> and Dutt<sup>26</sup> has been sufficiently successful to warrant a more extensive clinical trial. Since the publication of Carp's paper in 1927, only one additional report of the use of autohemotherapy has appeared in the American or English literature.

27. Morison, A. E.: Carbuncle and Its Treatment by Magnesium Sulphate, Brit. M. J. 1: 793, 1924.
28. Carp, L.: Circuminjection of Autogenous Blood in the Treatment of Carbuncles, Arch. Surg. 14: 868-890, 1927.
29. Dutt, C. R.: The Treatment of Carbuncles in the Out-Patient Department, Indian M. Gaz. 75: 75-76, 1940.
30. White, W. A., and Cooney, E. A.: A Non-Operative Treatment of Carbuncles, New England J. Med. 207: 398-402, 1932.
31. Pretty, H. G.: Bacteriophage in the Injection Treatment of Carbuncles and Allied Superficial Infections, Canad. M. A. J. 32: 24-29, 1935.
32. Ray, T. R.: The Non-Surgical Treatment of Carbuncles, J. Tennessee M. A. 26: 403-405, 1933.



5. In nondiabetic carbuncles, excepting deep lesions on the neck, x-ray and conservative methods are worthy of a trial. If there is not definite improvement in a few days, wide cruciate incision with under-cutting of the flaps is indicated.

6. Early radical surgery is the treatment of choice in all deep carbuncles of the neck.

7. Autohemotherapy is a method of therapy worthy of further clinical trial in the treatment of major carbuncles which are seen early.

8. Carbuncles in diabetic patients, excepting those on the face, do not respond well to conservative measures. Early radical surgery is indicated.

9. The value of the sulfonamides in the treatment of these lesions is not as yet determined.

#### REFERENCES

1. Light, R. A., and Sosman, M. C.: The Treatment of Carbuncles by the Roentgen Ray, *New England J. Med.* 203: 549-555, 1930.
2. Firor, W. B.: Roentgen Treatment of Carbuncles, *Am. J. Roentgenol.* 33: 71-74, 1935.
3. King, C. O.: Radiation Therapy of Carbuncles, *South. M. J.* 30: 903-906, 1937.
4. Lewis, R. W.: The Conservative Treatment of Carbuncles, *Ann. Surg.* 78: 649-659, 1923.
5. Hodges, F. M.: Roentgen Ray in the Treatment of Local Inflammations, Cellulitis and Carbuncles, *J. A. M. A.* 85: 1292-1294, 1925.
6. Andrews, G. C.: The Treatment of Boils and Carbuncles, *Am. J. Surg.* 6: 458-460, 1929.
7. Mitchiner, P. H.: The Prognosis in Carbuncles, *Lancet* 1: 507, 1935.
8. O'Brien, F. W.: Treatment of Severe Carbuncles by X-ray, *New England J. Med.* 220: 917-919, 1939.
9. Berman, J. K.: Therapy of Carbuncles, *Am. J. Surg.* 40: 419-425, 1938.
10. Fallis, L. S., and Hooker, D. H.: Carbuncles—Review of 166 Cases, *Urol. & Cutan. Rev.* 45: 196-199, 1941.
11. Carp, L.: The Treatment of Carbuncles, *Ann. Surg.* 86: 702-706, 1927.
12. McKittrick, L. S., and Root, H. F.: Diabetic Surgery, Philadelphia, 1928, Lea & Febiger, pp. 212-224.
13. Mowery, W. E.: Treatment of Carbuncles with the Actual Caustery, *Am. J. Surg.* 37: 170-172, 1923.
14. Jopson, J. H.: Carbuncles of the Back of the Neck, *S. Clin. North America* 3: 93-96, 1923.
15. Hosford, J.: Treatment of Boils and Carbuncles, *Brit. M. J.* 1: 400-402, 1938.
16. Kanavel, A. B.: Carbuncles—Infections of the Hand, Philadelphia, 1925, Lea & Febiger, p. 41-49.
17. Livingston, E. M.: New Principle in Surgical Treatment of Posterior Cervical Carbuncles, *Ann. Surg.* 84: 663-674, 1926.
18. Maes, U.: The Surgery of Diabetics as It Concerns Gangrene of the Lower Extremities and Carbuncles, *Surg., Gynec. & Obst.* 51: 700-704, 1930.
19. Lillenthal, H.: Carbuncles and Furuncles, *Am. J. Surg.* 50: 732-733, 1940.
20. Bailey, Hamilton: Ligature of the Angular Vein as a Preventive Measure in Facial Carbuncles, *Surg., Gynec. & Obst.* 46: 565-567, 1928.
21. Batson: Quoted by Gordon.<sup>23</sup>
22. Fraser, J.: Boils and Carbuncles, *Practitioner* 136: 350-366, 1936.
23. Gordon, D.: The Treatment of Boils and Carbuncles, *Am. J. Surg.* 36: 107-117, 1937.
24. Roberts, K.: The Treatment of Carbuncles About the Neck and Face, *Internat. Clin.* 3: 39-42, 1930.
25. Fellman, M.: The Treatment of Carbuncles With Short Wave Diathermy and Caustery Puncture, *Am. J. Surg.* 32: 467-468, 1936.
26. Beling, C. A., and Abel, A. R.: The Treatment of Furuncles, Carbuncles and Abscesses of Staphylococcal Origin With Thiozole Derivatives of Sulfanilamide, *Am. J. Surg.* 50: 255-266, 1940.

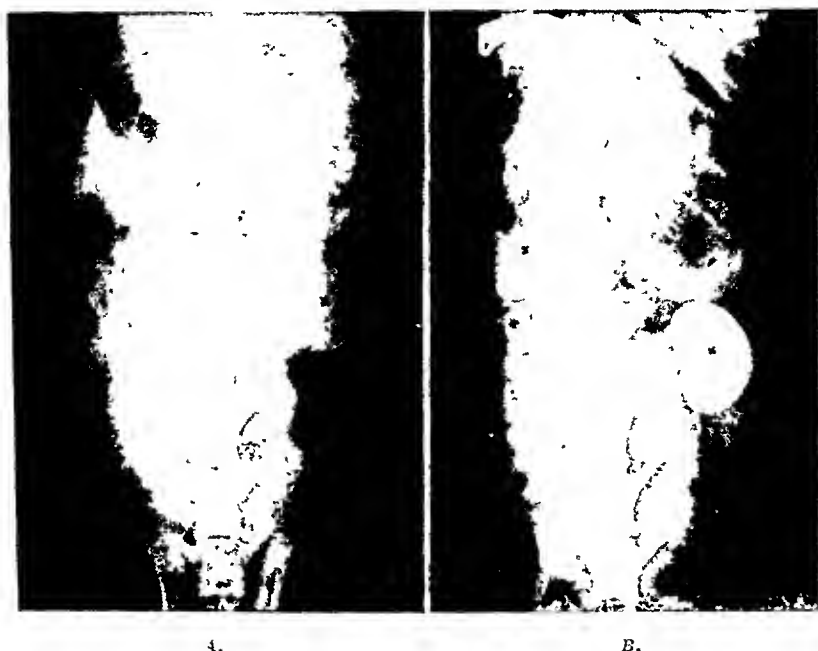


Fig 1—A, Rabbit No. 6, Table I, before injection of thioisomol. Faint shadow in left kidney. B, Rabbit No. 6, after injection of thioisomol. Distinct shadows in both kidneys.

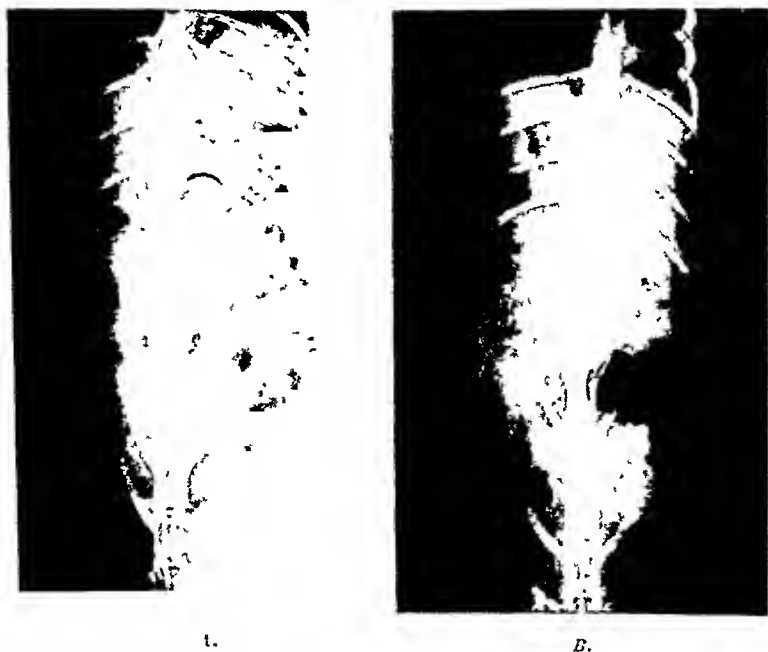


Fig 2—A, Rabbit No. 9, Table I, before injection of thioisomol. No shadow of kidneys. B, Rabbit No. 9, after injection of thioisomol. Distinct shadow of both kidneys.

## LOCALIZATION OF BISMUTH IN THE KIDNEY

H. KROLL, PH.D., ROBERT A. ARENS, M.D., S. MESIROW, M.D.,  
S. F. STRAUSS, M.D., AND H. NECHELES, M.D., PH.D., CHICAGO, ILL.

(From the Departments of Gastrointestinal Research and Roentgenology, Michael Reese Hospital)

IT IS well known that bismuth compounds as used in the therapy of syphilis may be concentrated in the kidneys, and analyses carried out on experimental animals and on human beings have been reported from various laboratories.<sup>1-5</sup>

In our work on the localization of abscesses<sup>6-8</sup> we have also used the water-soluble bismuth compound thiobismol\* (sodium bismuth thioglycollate). The experiments were conducted on brown Belgian rabbits who received varying amounts of thiobismol in one dose or in divided daily doses by intramuscular injection. Various organs were analyzed for bismuth contents by the method of Lehman, Richardson, and Hanzlik.<sup>9</sup>

The first group of rabbits were apparently normal animals from our stock. Control films of the kidneys were taken and then thiobismol in doses varying between 40 and 180 mg. was injected. Twenty-four hours after the last injection a roentgenogram was taken; in a number of animals films were taken after every injection. All films were taken with the animal on its back, and with the same focal distance, tube, and screen. In all six rabbits of this group a distinctly increased bismuth content was found in the kidneys as compared to other organs. In rabbits 5 and 6 (see Fig. 1) the substance of the kidney was found distinctly visible on the x-ray film twenty-four hours after the last injection of thiobismol. The kidneys of these rabbits contained relatively large amounts of calcium on chemical analysis. This observation may explain the visualization of one kidney in the control film of rabbit 6 (see Fig. 1). In rabbit 5 one kidney only appeared on the x-ray picture following the thiobismol injection, and autopsy revealed the presence of only one organ, a not quite infrequent observation in rabbits. In rabbits 1 to 4 the kidneys were not visualized.

The presence of large amounts of calcium salt in the kidneys of two rabbits indicated an abnormal condition of this organ which possibly was responsible for the accumulation of the bismuth. Therefore, in the next group of rabbits (7 to 10), an attempt was made to produce a pathologic condition of the kidney by the intravenous injection of 2 to 4 c.c. of ethylene glycol on subsequent days. Two days later thiobismol was injected and twenty-four hours after the last injection x-ray films

\*Generously supplied by Dr. O. Kamm, Parke, Davis & Company.  
Received for publication, Dec. 4, 1941.

were taken. In three of these four animals a distinct shadow of both kidneys was observed. Chemical analysis showed the presence of relatively large amounts of bismuth in the kidneys (see Fig. 2), but no significant amount of calcium was found. In the fourth rabbit (No. 10) repeated films gave inconclusive results, because large amounts of gas obscured the entire abdomen.

A histologic study of the kidneys of the animals treated with ethylene glycol and with ethylene glycol and thiobismol showed severe lesions of the glomeruli and tubules.\*

#### SUMMARY AND CONCLUSIONS

Our experiments indicate that the kidney of the normal rabbit does not accumulate amounts of thiobismol sufficient for its visualization on the x-ray film. On the other hand, in rabbits with pre-existing kidney pathology, as evidenced by significant amounts of calcium in the kidneys, as well as in rabbits whose kidneys had been damaged by ethylene glycol, the injected thiobismol was accumulated by the diseased kidneys to such a degree that they acquired sufficient radiopaqueness to stand out very distinctly on the x-ray film.

It is known that the administration of thiobismol per se to the human being or animal can be followed by kidney damage,<sup>10</sup> and that the administration of this substance to patients with kidney disease is dangerous. We know from the studies of others that, in the human being and in animals, injected bismuth is excreted in the urine in large amounts,<sup>11</sup> and we had evidence of this in about half of our films by a dense bismuth shadow of the filled urinary bladder. We feel that our observations are worth-while reporting to give another warning against the use of thiobismol or similar compounds in the presence of damaged kidneys, and we want to draw the attention of the clinician to the possibility of demonstrating such conditions on the x-ray film. The production of radiopaqueness of the entire kidney would certainly be a desirable method for the detection of intrinsic or extrinsic pathology of this organ. The possibility is suggested, therefore, of the future use of this method in the human being, for instance, in the case of one-sided surgical kidney disease. The pathologic kidney would store bismuth, and therefore concretions, cysts, tumors, etc., would stand out on the x-ray film. The healthy kidney would not store bismuth and would not be damaged by the ordinary therapeutic doses of bismuth, which have been established as safe in a long experience in the treatment of syphilis. This problem is under investigation.

#### REFERENCES

1. Fishback, H. R., and Fishback, D.: Experimental Studies on Long Continued Administration of Bismuth; Summary Form, *J. Lab. & Clin. Med.* 23: 127-129, 1937.

\*Histologic study made by Dr. Max Appel, Department of Pathology, Michael Reese Hospital.

TABLE I  
LOCALIZATION OF BISMUTH IN THE KIDNEY

RABBIT NO.	C.C. ETHYLENE GLYCOL I. V.			X RAY OF KIDNEYS	MG. THIOBISUL I. V.			X RAY OF KIDNEYS 24 HOURS AFTER LAST INJECTION	REMARKS
	NO. OF DAYS	INDIVID. CAL DOSE	TOTAL DOSE		NO. OF DAYS	INDIVID. CAL DOSE	TOTAL DOSE		
1				Negative	1	40	40	Negative	
2				Negative	12	15	180	Negative	
3				Negative	11	15	165	Negative	
4				Negative	11	15	165	Negative	
5				Negative	1	80	80	Distinct shadow, left kidney	No right kidney found at autopsy. Calcium in kidney
6				Faint shadow in left kidney	12	15	180	Distinct shadow, both kidneys (See Fig. 1)	Calcium in kidneys
7	2	†	8	Negative	8	15	120	Distinct shadow, both kidneys	
8	2	†	8	Negative	6	15	90	Distinct shadow, both kidneys	
9	2	2 and 4	6		6	15	90	Distinct shadow, both kidneys (See Fig. 2)	
10	2	†	8	Negative	8	15	120	Gas in intestines on all films Visualization of kidneys doubtful	

# UNILATERAL HYPERTROPHY OF THE MASSETER MUSCLE

ROBERT J. COFFEY, M.D., M.S. (IN MED.), PH.D. (IN SURG.),  
WASHINGTON, D. C.

**I**NASMUCH as the masseter muscle contributes importantly to the configuration of the face, a malformation or tumor of this structure results in an early and conspicuous deformity. Such a lesion may be easily mistaken for a mixed tumor of the parotid gland, a salivary retention cyst, or an adamantinoma.

The rarity of primary tumors of the masseter is revealed by my failure to collect more than 9 cases in a review of the literature. Dudon,<sup>1</sup> in a thesis on this subject, reported the occurrence of 2 cases of cystic sarcoma and 1 case in which a fibrochondroma was identified. King<sup>2</sup> described a case of severe trismus in which the resected muscle had been almost totally converted into fibrous tissue. Tatum's<sup>3</sup> case of recurring fibroma of the masseter was undoubtedly an instance of fibrosarcoma. A case of rhabdomyosarcoma was reported by Larue.<sup>4</sup> Pantaloni<sup>5</sup> observed the occurrence of a primary angioma of the masseter in 1 case and he collected 2 similar cases from the literature.

Nonneoplastic affections of this muscle are of such frequency as to deserve mention. Dudon<sup>1</sup> described 2 cases of hydatid cyst of the masseter and, in addition, he mentioned the involvement of this muscle in tuberculosis, trichinosis, actinomycosis, and myositis ossificans. Margarot, Rimbaud, and Ravoire<sup>6</sup> presented 3 cases of gumma of the masseter, in all of which the tumefaction disappeared with antisyphilitic therapy. An interesting case of a cyst situated in the right masseter muscle was reported by Beco.<sup>7</sup> He identified several small ranulas in the adjacent tissue, and consequently he concluded that it was a retention cyst of an accessory portion of the parotid gland. Duroux<sup>8</sup> described a case of asymptomatic bilateral hypertrophy of the masseter, the nature of which was undetermined.

## CASE REPORT

W. K., white male, aged 19 years, was seen in consultation with Thomas Monks, D.D.S., on March 5, 1941, because of a tumor of the right jaw. In 1936 members of the patient's family observed an enlargement of the right side of his face. Earlier photographs reveal no facial asymmetry. During the past year the swelling reached sufficient size to become a source of embarrassment to the patient, and he had complained of mild discomfort in the region of the tumor. Except for a rather unusual fatigue associated with prolonged chewing, mastication was not interfered with. Not infrequently the buccal mucous membrane on the right side was traumatized during mastication. No facial tic existed. Dental examination revealed the presence of four impacted wisdom teeth.

2. Sollman, T., Cole, H. N., and Henderson, K.: Clinical Excretion of Bismuth. Excretion of Sobismol and of Some Other Bismuth Preparations for Oral Administration, *Arch. Dermat. & Syph.* 37: 993-1002, 1938.
3. Sollman, T., Cole, H. N., and Henderson, K.: Clinical Excretion of Bismuth; Autopsy Distribution of Bismuth in Patients after Clinical Bismuth Treatment, *Am. J. Syph., Gonorr. & Ven. Dis.* 22: 555-583, 1938.
4. Sollman, T., and Henderson, K.: Bismuth Studies; Bismuth Distribution in Dogs Following Intramuscular Injection of Single Dose of Various Bismuth Preparations, *Am. J. Syph., Gonorr. & Ven. Dis.* 22: 739-756, 1938.
5. Brabant, H.: Recherches sur l'Elimination du Bismuth par le Rein et les Glandes Salivaires, *Arch. internat. de pharmacodyn. et de therap.* 63: 397, 1939.
6. Strauss, S. F., Neuwelt, F., Rovner, L., and Necheles, H.: A New Method for Detection of Hidden Abscesses, *SURGERY* 4: 930, 1938.
7. Kroll, H., Strauss, S., and Necheles, H.: Concentration and Detection of Dye in Abscesses, *Proc. Soc. Exper. Biol. & Med.* 43: 228-234, 1940.
8. Kroll, H. H., Strauss, S. F., and Necheles, H.: Studies on the Detection of Abscesses and Tumors. III. Concentration and Detection of a Radioactive Substance in Abscesses, *J. Lab. & Clin. Med.* 27: 50-53, 1941.
9. Lehman, A. J., Richardsou, A. P., and Hanzlik, P. J.: Improved Procedures for Estimating Bismuth in Body Fluids and Tissues, *J. Lab. & Clin. Med.* 21: 95-97, 1935.
10. Eitzen, A. C.: Toxic Effects of Bismuth, With Especial Reference to Renal Damage and Report of Case of Anuria, *Am. J. Syph., Gonorr. & Ven. Dis.* 21: 674-678, 1937.
11. Sollman, T., Cole, H. N., and Henderson, K.: Clinical Excretion of Bismuth; Urinary Excretion of Bismuth after Clinical Intramuscular Injections of Sodium Iodobismuthite (Sodium bismuth iodide, Iodobismitol) and Sodium Bismuth Thioglycollate (Thiobismol), *Am. J. Syph., Gonorr. & Ven. Dis.* 21: 480-491, 1937.

On examination a soft, noncystic, and slightly tender mass, measuring 3 by 4 cm., was both visible and palpable immediately above and medial to the angle of the jaw on the right side. No palpable enlargement of the right parotid gland was found. Simultaneous palpation from within the oral cavity and on the surface revealed that the major portion of this mass presented externally. Saliva flowed freely from the parotid duct on the involved side. A roentgenogram of the right mandible showed no evidence of disease of the bone. The Kahn test was negative. A tentative diagnosis of tumor or retention cyst of the facial process of the parotid gland was made.

On March 13, 1941, under intratracheal nitrous oxide anesthesia, a 4 cm. incision was made along the superior border of the mandible. On exposure of the masseteric fascia, the underlying mass resembled thyroid tissue as seen through its intact capsule. The fascia was incised, and longitudinally disposed muscle fibers were encountered. Assuming that these fibers were overlying the tumor, the dissection was carried deeper into the muscle until finally the buccal mucosa was reached. It was



Fig. 3.—Photograph taken five months postoperatively showing diminution in the size of the hypertrophied masseter muscle.

then apparent that the mass consisted of a greatly hypertrophied masseter muscle. A biopsy of this tissue was submitted for pathologic examination to Dr. Vincent Dardinski who reported: "The tissue is composed of striated muscle, the individual fibers of which are thicker than normal; whether this can be construed as being a pathologic process is difficult to say because of the absence of any other pathologic changes [Fig. 1]."

One month after primary healing of the incision, it was noted that contraction of the jaws caused a conspicuous protrusion of the mass, probably as a result of herniation of the muscle fibers through the sutured masseteric fascia (Fig. 2). A slight but not unusual prominence of the corresponding muscle on the opposite side was observed. Although the dental surgeon was of the opinion that the impacted wisdom teeth were in no way related to the muscle hypertrophy, these teeth were subsequently extracted. The patient was advised to avoid unnecessary use of the masseters, as in gum chewing, and to confine his mastication to the uninvolved side





Fig. 1.—Photomicrograph of section of muscle biopsy showing hypertrophy of the individual fibers; no evidence of inflammation is present. ( $\times 515$ .)



Fig. 2.—Photographs showing the size of the mass (A) with jaws relaxed, and (B) with jaws contracted.

## Editorial

---

### The Use of Refrigeration Combined With Vasodilatation to Preserve Vitality in a Relatively Ischemic Extremity

THE WORK of Allen and his associates on the use of refrigeration as a preliminary to amputation in older individuals with primary degenerative arterial disease in which gangrene is imminent has done much to lower the mortality rate in these poor-risk patients. They have shown that in older patients with impending arteriosclerotic gangrene, with or without diabetes, the application of a tourniquet to the extremity rendering it totally ischemic combined with refrigeration of the extremity will not only retard bacterial invasion in such an extremity, but will permit amputation to be done safely without the use of any further anesthesia. Nothing is more dramatic than to see the ease with which an amputation can be done in such a poor-risk patient without anesthesia and to observe the uneventful convalescence which he has postoperatively.

Whereas these contributions of Allen and his associates in elderly patients with primary arterial disease of an extremity are of inestimable value, it is our opinion that refrigeration is probably of greater value in younger individuals whose vascular system is otherwise normal, but in whom there is an interference with the blood supply as a result of trauma. In these instances, refrigeration should be used not as a preliminary to amputation but in an attempt to decrease the metabolism of the part sufficiently so that the impoverished blood supply is capable of maintaining the viability of the extremity. Previously, in the presence of interference with vascularity of the extremities it has been the popular practice to apply heat; and yet according to the investigations of Allen, Freeman, Brooks, and Duncan, the use of heat in this way is probably the worst thing that can be done. As has been demonstrated by Brooks and Duncan, the production of a total ischemia in a rat's tail results in massive necrosis occurring within four hours if the tail is maintained at a temperature of  $40^{\circ}\text{C}$ . On the other hand, a similar degree of ischemia does not result in serious damage to anemic tissues for as long as four days if the temperature is maintained at  $4^{\circ}\text{C}$ .

Whereas it is extremely desirable, by decreasing the environmental temperature, to decrease the metabolism of the cells of the part to a sufficient degree that vitality can be maintained with an otherwise inadequate blood supply, it is equally undesirable to decrease further the blood supply of the extremity as a result of vasoconstriction produced by the application of cold. Therefore, it is obvious in those cases in

as much as possible. Definite diminution in the size of the hypertrophied masseter is evident in a photograph taken five months postoperatively (Fig. 3).

#### COMMENT

The occurrence of this heretofore unreported condition of unilateral hypertrophy of the masseter muscle presents several problems. The cause of the hypertrophy in this case was undetermined. No dental or orthopedic basis for a compensatory hypertrophy was discovered. Evidence of an inflammatory myopathy was lacking in the histologic sections of the muscle biopsy. No evidence of syphilitic or tuberculous involvement of the muscle existed. The clinical diagnosis of this rarity, in retrospect, could have been made by combined intraoral and external palpation of the contracted muscle. Conservative treatment is recommended. Habit tics, gum chewing, and such actions that unnecessarily exercise the involved muscle should be avoided. Surgical resection of the muscle, in whole or in part, would probably only aggravate the facial deformity and, in addition, would expose the patient to the risk of suffering an injury to the facial nerve and the parotid duct. X-ray therapy of the involved muscle is mentioned only to condemn it.

#### REFERENCES

1. Dudon, H.: *Tumeurs primitives du muscle masseter*, Bordeaux Thèses 135: 60 pp., 1904.
2. King, K.: Case of Fibroid Tumor of the Masseter Muscle, *Lancet* 2: 833-834, 1875.
3. Tatum: Quoted by Holmes, T.: *A System of Surgery*, New York, 1870, Wm. Wood & Co., vol. 3, p. 640.
4. Larue, F. A.: Tumors of the Masseter, With Special Reference to Sarcoma, *Tr. South. Surg. & Gynec. A.* 12: 390-394, 1899.
5. Pantaleoni, C.: Angioma primitivo del masseter destro, *Bull. d. sc. med., Bologna* 4: 442-452, 1904.
6. Margatot, J., Rimbaud, P., and Ravoire, J.: La syphilis du masseter à propos de trois observations inédites, *Ann. d. mal. vén.* 34: 159-167, 1930.
7. Beco, L.: Sur un cas de tumeur du masseter, *Presse oto-laryngol. belge, Brux.* 2: 508-511, 1903.
8. Duroux, M.: Hypertrophie Musculaire Bilatérale des Masseters, *Lyon med.* 104: 1335-1336, 1904.

# Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

## RECENT SURGICAL PHYSIOLOGY OF THE PANCREAS\*

SIGMUND A. SIEGEL, M.D., NEW YORK, N. Y.

*(From the Department of Surgery, New York University College of Medicine, and the Surgical Division of Sydenham Hospital)*

### INTRODUCTION

IT IS only recently that a new impetus has been given to the re-examination of the physiology of the pancreas. As is true of all research, this stimulus has not resulted from any one factor, but from the gradual accumulation of knowledge opening new avenues of thought. The abstract knowledge finally succeeds in supplying the tools needed for the reinvestigation of a problem which formerly had been studied by the tools then at hand, but allowed to end at a certain point. It is amazing that the most important digestive organ in the body is the "dark continent" of the intestinal tract. The appearance of a pure chemical stimulant and a slight change in approach has resulted in new and successful means of studying pancreatic function. A functional test has also appeared. The most recent and still controversial phase of study is the evaluation of a new lipotropic hormone. With the accurate determination of blood enzymes, the diagnosis of pancreatitis has been simplified. The importance of this is well understood. In the near future the study of pancreatic function promises to make strides equal to that of the other organs of the body. Several reports of evaluations of the result of surgery in hyperinsulinism have been published. Pancreatic secretions continue to be studied in broad abstract aspects.

### HYPERINSULINISM

Harris<sup>1</sup> in 1924, two years after the discovery of insulin, predicted a syndrome due to hyperfunction of the islands of Langerhans, analogous to hypo- and hyperthyroidism. Subsequently, he reported five clinical but obvious cases of hyperinsulinism. In 1927 Wilder and co-workers<sup>2</sup> reported the first proved case which was due to carcinoma of the islet tissue of the pancreas with metastases. Analysis of the metastatic tissue revealed a high insulin content. Symptoms began three hours and twenty minutes after lunch, with a blood sugar volume of 55 mg. per cent.

\*Read before the Graduate Surgical Seminar, New York University College of Medicine, Dec. 11, 1941. Dr. Arthur M. Wright, Director.

which refrigeration is used to decrease the temperature of the part and thus decrease its metabolism in a relatively ischemic extremity, that vasoconstriction must be prevented. As has been repeatedly shown by many, vasoconstriction is best prevented by blocking the vasoconstrictor impulses which are carried over the sympathetic nervous system. This is probably accomplished best by repeated chemical sections of the sympathetic ganglia by means of novocain or by prolonged chemical section by means of novocain and alcohol.

The correct amount of refrigeration in the younger individuals in whom the maintenance of viability of the extremity is desired is more difficult to determine than that in the individual in whom refrigeration is used as a preliminary to amputation. In the latter instance, the extremity is rendered totally ischemic by means of a tourniquet, and the extremity is packed in ice. In the former instance, this degree of refrigeration is undesirable and detrimental. For that reason it is imperative that the temperature be carefully controlled. In order to prevent actual injury to the skin by too intimate contact of the refrigeration medium, it is desirable, if the cooling is accomplished by means of ice bags, that the extremity be wrapped in one or two layers of thin sheet wadding. It is preferable, however, that a refrigerating boot into which cooled air can be introduced be used. The degree of refrigeration which is necessary probably varies in different cases. Generally a Fahrenheit temperature of forty to fifty degrees is considered optimum. This can and should be maintained for long periods of time. It is important that when the refrigeration is discontinued it be done gradually, that is, that there be a gradual elevation in the temperature over a period of a number of days. In this way massive edema of the part can be obviated.

—*Alton Ochsner, M.D.*  
New Orleans, La.

creatic juice entering the intestine, normal fat absorption took place. This was due, in all probability, to gastric, intestinal, and biliary lipase, and bacterial activity in the intestine. Kennard<sup>7</sup> reported a papillary cystadeno-carcinoma of the pancreas which showed mild diabetes post-operatively for ten months, the total follow-up period. Burtness and co-workers<sup>8</sup> report a case of hyperinsulinism in which oral and intravenous dextrose and insulin tolerance curves were used with considerable aid in the diagnosis. Following removal of the adenoma, the same tests revealed a decreased tolerance to glucose. Thus it is seen that the surgery of hyperinsulinism is well advanced.

#### FATTY LIVER IN RELATION TO THE PANCREAS

The relationship between the pancreas and fatty liver has been known for several years. However, it is still incompletely understood. Fisher<sup>9</sup> in 1924 showed that insulin alone could not adequately maintain depancreatized dogs nor enable the animals to completely recover their well-being. They were unable to live for more than a short while. The most relative change seen at post-mortem was an associated marked fatty infiltration of the liver. Since then, it has been definitely shown and repeatedly confirmed that if raw pancreas was added to the diet, in addition to insulin, the animals could survive. Furthermore, they could live for long periods of time and these changes did not occur. Hershey<sup>10</sup> in 1930 showed that 10 Gm. of lecithin added to the daily diet would prevent the fatty infiltration of the liver. Best and Huntsman<sup>11</sup> subsequently identified the active ingredient as choline. Pancreatic extract contains in addition to the various enzymes, only a small amount of choline, which Dragstedt<sup>12</sup> showed was not sufficient to influence the liver. He has been the most active proponent in favor of lipocaic as a hormone. This substance is contained in an alcoholic extract of beef pancreas. Its effectiveness is not due to its choline content since liver or brain, which contain large amounts of choline, are not effective. The effective amount of choline is 2 Gm. per day, whereas 100 Gm. of raw pancreas, the effective dose, has only one-sixteenth the required amount of choline. Dragstedt holds the external pancreatic secretion to be important, but not the factor in the prevention of fatty liver. He found that, in depancreatized dogs on a balanced diet and sufficient insulin to control urinary sugar, fresh active pancreatic juice by mouth did not cause the disappearance of fatty infiltration of the liver and return of blood lipids to normal. After six to eight weeks, the requirements for insulin are reduced to two to three units daily; the sensitivity to insulin meanwhile increases greatly. The obvious explanation is decreased glycogen storage in the liver, which occurs concurrently. Progressive emaciation, weakness and enlargement of the liver occur. If lipocaic is given to the animal in this stage, the liver promptly decreases in size, and the architecture returns to normal.

One hour later it was 27 mg. per cent, the patient meanwhile becoming stuporous. Whipple and Frantz<sup>3</sup> in 1935 established the diagnostic triad of symptoms: (1) nervous or gastrointestinal symptoms appearing in a fasting state; (2) blood sugar readings of 50 mg. per cent or less; and (3) immediate relief by administration of glucose. The symptomatology is rendered more complex by the known interrelation of the pituitary, thyroid, adrenal, liver, and sympathetic nervous system in sugar metabolism.

The statistics of operative results are truly impressive. In Whipple's<sup>4</sup> collected series of 82 cases there was a mortality of 16 per cent, or thirteen patients. Sixty-two of the remaining sixty-nine were cured of their spontaneous hypoglycemia. These figures show further improvement when we consider that a second operation or autopsy report will often disclose a tumor in a portion of the pancreas which was not obvious previously. David<sup>5</sup> says, "this would strongly imply that it is exceedingly hazardous to assume with careful selection of patients with hypoglycemia that a tumor of the islet cells is not present." A blind subtotal resection of pancreatic tissue may afford relief in the indicated case by revealing a tumor well imbedded, by revealing hyperplasia of islet tissue, or by decreasing the amount of insulin-secreting cells. For this purpose it is estimated that from two-thirds to four-fifths must be removed, allowing 60 to 90 Gm. as the normal weight of the pancreas. In David's collected cases he reports on a series of patients in whom no tumor was found at operation, but a portion of the pancreas was resected instead. In twenty-two the tumor was revealed at pathologic examination. The results were successful as one would expect from the removal of the tumor. In another group of 18 cases having 8 to 28 Gm. removed where normal pancreatic tissue or hyperplasia was found, eight patients were unimproved and four died. However, in a third group of 17 cases strictly satisfying the criteria of the disease where 35 to 60 Gm. were removed, eleven patients were cured, one improved, four unimproved, and one died. These last figures are most impressive and seem to indicate a definite avenue for future progress. Proper surgical exploration requires competent examination of the anterior surface of the pancreas, including reflection of the descending portion of the duodenum to expose the head of the pancreas adequately, and, if necessary, incision of the gastrocolic ligament or transverse mesocolon.

Whipple and Banman<sup>6</sup> report a definite tendency to a diabetic glucose tolerance curve in patients with hyperinsulinism due to pancreatic adenomas, both before and after removal. Conceivably, the hyperactive adenoma has depressed the function of the remaining islet tissue. They place more faith in fasting blood sugar figures. Conversely, in 3 cases where three-fourths of the pancreas was removed the same tendency was manifest, but apparently the enormous reserve corrected the tolerance within two years. In several cases, after operation with no pan-

from five and five-tenths grams of raw pancreas which will accomplish the same when given by mouth daily and has only 100 mg. of choline. Obviously, in this fraction, it is not the choline which is curative. Kauer and Glenn<sup>17</sup> studied ten dogs with 17 per cent to 84 per cent of their pancreas removed. One animal with 66 per cent removed had a fatty liver transiently. Another with 71 per cent removed showed this definitely. One with 84 per cent removed did not show the usual fatty degeneration, but it developed diabetes. In congenital pancreatic steatorrhea or fibrosis and atrophy of the pancreas, the only tissue affected is the acinar tissue, and not the islets, yet fatty liver is a prominent feature. Cole and Howe<sup>18</sup> report a case with a severe degree of focal necrosis, atrophy, and fibrosis of the pancreas involving three-fourths of the pancreas with normal islet tissue and fatty infiltration of the liver. Their opinion was that lipocaic was effective, but had not established itself since vitamins and lecithin were equally effective.

The Council on Pharmacy and Chemistry of the American Medical Association,<sup>19</sup> in consideration of lipocaic, suggests that further investigation will be required to identify the active substance. Also, its use is considered highly experimental. Finally, since the frequent association of varying degrees of pancreatitis with gall bladder disease is now well-recognized, it may be deemed increasingly important to protect the liver with lipocaic or pancreatic juice.

#### SECRETIN

A study of the external pancreatic function of the pancreas has in the past been prevented by seemingly insurmountable obstacles. The secretion was inaccessible, a standard stimulus was lacking, and the juice finally obtained was invariably grossly contaminated with food, gastric contents, and the chemical stimulants used. With the introduction of secretin by Hammarsten and co-workers,<sup>20</sup> a potent pancreatic stimulus, without histamine or allergens, was made available. Diamond and his group<sup>21</sup> have continued the work in this country. The results have been so definitive that the secretin test may now rank to be as informative as the gastric test meal. A double gastroduodenal tube is used to collect the pancreatic juice and remove gastric secretions. This last is important in preventing the normal physiologic secretin mechanism from operating while the test is being performed. The recent work in this subject has been reported by Diamond and Siegel<sup>22</sup> who have studied pancreatic volume, bicarbonate, amylase, trypsin, lipase, and blood amylase and lipase. With experience, there are no difficulties to the method. Fully one-half of the tests performed have been done in the office. Essentially, a double tube is passed so that one portion remains in the stomach and another remains in the duodenum. Gastric and duodenal contents are removed with a suction of 50 mm. of water until a basal flow is established for twenty to twenty-five minutes. Secre-



Also, the animal is no longer sensitive to insulin and indeed requires a larger amount of insulin to balance urinary sugar.

McHenry and Gavin<sup>13</sup> studied fat metabolism and synthesis in relation to pancreatic and liver extracts. They found a marked increase in body and liver fat containing a large amount of cholesterol due to synthesis in rats on a fat-free diet when they fed a liver fraction containing pantothenic acid and factor W. The above could also be accomplished by a diet containing thiamine but low in choline. The fatty liver of the thiamine diet would easily be prevented by feeding choline. The type due to the liver fraction was prevented by feeding lipocaine but not by choline. It was thus obvious that in this experiment the lipocaine did not function by virtue of its choline content, but perhaps because of its protein content. Brewer's yeast was incompletely effective in preventing fatty liver of this type, while rice-polishings concentrate was completely effective. Admittedly, the fatty liver in the depancreatized animals is not definitely similar to that produced by the liver factor. Since rice polishings and yeast will prevent the fatty liver in these experiments, it is suggested that lipocaine is not specific enough to be called a hormone. Montgomery and collaborators<sup>14</sup> made an attempt to determine whether lack of the external secretion of the pancreas caused fatty disease of the liver, since both pancreatectomized dogs and pancreatic duct ligated dogs invariably developed fatty infiltration. In a group of sixteen dogs, eight were ligated, of which four were controls, and eight had pancreatectomy performed, of which three were controls. The treated group were first fed raw pancreas until their strength returned and then were fed pancreatic juice from animals with Elman-McCannan fistulas. Twenty weeks later the control group had fatty livers in which the fatty acid content varied from 15.1 per cent to 20.5 per cent, whereas, the others showed 3.11 per cent to 7.0 per cent. Both ligated and pancreatectomized groups were essentially the same. From these experiments one would conclude that it is the external pancreatic secretion which maintains normal lipid level of the liver. However, there is still the possibility that the final effective product is the result of the interaction of pancreatic secretion and intestinal mucosa. The authors feel that it is not a pancreatic hormone. Entenman and co-workers<sup>15</sup> found that the cholesterol, phospholipid, and total fatty acid of the blood can be raised from its low level and be maintained at a normal figure in duct-ligated and pancreatectomized dogs by the daily ingestion of pancreatic juice. However, Entenman and Chaikoff<sup>16</sup> have shown that 36 mg. of choline per kilogram per day are sufficient to prevent the deposition of abnormal amounts of lipids in the livers of depancreatized dogs maintained on insulin even up to five months. In their studies with the feedings of raw pancreas, 250 Gm. contain 575 mg. of choline and it may be that chemical which exerts the curative or preventative effect. They have a pancreas fraction of one gram, derived

creatic tissue give values below that of serum. The concentration of bicarbonate ions occurs in the cells and is derived from plasma. Hug,<sup>25</sup> in studying secretion of sulfanilamide by the pancreas after secretin or pilocarpine, found it to vary between 73 to 77 per cent of the blood concentration. Thomas and Crider<sup>26</sup> studied the secretagogue effect of products of protein digestion on the pancreas. They found the peptones powerful stimuli of certain functions of the gland. While the volume was increased, it was inferior to the action of hydrochloric acid. The active secretagogue was not identified, but the purified proteoses and some amino acids were effective. Since the result was a different secretion than that from secretin, it is suggested that the mechanism is nervous and similar to "vagus juice," "pilocarpine juice," "psychic secretion" and that following mechohyl. Comfort and Osterberg<sup>27</sup> studied a series of pancreatic stimulants with the purpose of determining the most practical for studying the pancreatic juice. Vitamin A and starch did not produce any apparent effect. Mecholyl was as potent but a more uniform stimulant than casein, fat, or prostigmine. Secretin was the choice stimulant for the study of fluid and bicarbonate output, and gave as satisfactory information as the others about the enzymes. Secretin and mecholyl gave the maximum "all out" stimulation since the hormonal and nervous mechanism was utilized. This latter combination appeared the most satisfactory to study the maximum output of the gland. The injectable stimulants have obvious advantages over the foods as they avoid contamination and are measured more accurately.

#### ACUTE PANCREATITIS

Claude Bernard<sup>28</sup> in 1855 was able to produce typical acute pancreatitis with the injection of bile and olive oil into the pancreatic duct. Opie<sup>29</sup> in 1903 demonstrated the relation between an impacted stone in the ampulla of Vater and acute pancreatitis. His was the first successful attempt to cause this disease by lodging a stone in the ampulla so that the biliary system and pancreatic ducts were converted into a continuous channel. From that time, it has been conventional to regard as the "modus operandi" the activation of trypsinogen in the pancreatic ducts by bile. Following this train of thought, the now active enzymes proceed to digest the pancreatic cells and supporting network with the liberation of additional trypsin. Eventually, blood channels are opened with hemorrhage and infarction. As a result the gland is torn and additional acini are opened with the liberation of further enzymes continuing the cycle. Cameron and Noble<sup>30</sup> did much to settle the anatomic basis for the reflux of bile by impacting a stone in the ampulla and injecting a colored dye. In 74 per cent they found a continuous channel. Reflux of bile may not only occur due to the impassable stone, but it is now generally felt that dyskinesia of the ampulla or local edema of the duodenum may be a prominent factor. Simple variations in the pressure

tin is then injected intravenously in dosage of 0.75 mg. per kilogram of body weight. Specimens are collected at intervals for sixty minutes. Immediately following the injection, a sharp increase in the flow of pancreatic juice is obvious, reaching a maximum in ten minutes and gradually declining to the basal level in sixty to eighty minutes. The total output of volume, bicarbonate, and enzymes is tremendously increased though, due to dilution, the concentration of the enzymes falls. It has been established that many cases of chronic cholecystitis have chronic pancreatitis. Of seventeen patients studied, those with complications had abnormal tests. Acute pancreatitis gave grossly abnormal results comparable with the degree of involvement. In addition, the degree of recovery could be followed. In obstructive jaundice the test was of special value. Carcinoma of the head of the pancreas gave very low figures. With atresia of the common duct, or carcinoma of the bile duct the amounts were from slightly diminished to normal. Also studied were cysts of the pancreas, cirrhosis of the liver, toxic hepatitis, acute yellow atrophy of the liver, steatorrhea, diabetes, and a miscellaneous group. The tests revealed many instances of unsuspected pancreatic disease and showed decreased pancreatic function in many diseases which, heretofore, were not thought to affect the pancreas.

#### PANCREATIC SECRETIONS

Tucker and Ball<sup>23</sup> attempted to determine the role of carbonic anhydrase in bicarbonate secretion by the pancreas. If this enzyme catalyzes the change from carbon dioxide to bicarbonate, its destruction should markedly influence the rate of alkali formation. Accordingly, sulfanilamide and thiocyanate were administered while the pancreas was under maximum stimulation and output following secretin. Results indicate that sulfanilamide did not inhibit pancreatic flow or bicarbonate concentration, though the concentration in the cells was in the usual ratio between that of the blood and pancreatic juice. To explain contradictory reports, it was found that extracted carbonic anhydrase was inhibited by sulfanilamide when the enzyme was prepared from pancreas or other tissues. However, in the cells, sulfanilamide was without influence on the pancreatic secretion. As the output of bicarbonate by the gland was larger than could be explained, at least part of the bicarbonate must arise from cell metabolism. Thiocyanate gave similar results until toxic doses were given. Ball and collaborators<sup>24</sup> injected intravenously bicarbonate made from radioactive carbon. The radioactive bicarbonate was increased in the juice four to five times that of the serum. Since radioactive sodium is approximately the same concentration in the pancreatic secretion as in the plasma and the total carbon dioxide has the same ratio as the radioactive bicarbonate, the authors conclude the metabolic carbon dioxide is not the source of bicarbonate. Analyses of total carbon dioxide of pan-

in blood enzymes. When the pancreatic duct was tied and bile was injected distally, the rise in blood amylase was obvious in five to ten minutes. This was seen mainly in portal blood and to a lesser degree in the lymph of the thoracic duct. Edmouson and Fields<sup>41</sup> reported a patient with acute pancreatitis who showed shock and tetany. Since the carbon dioxide combining power was forty-seven volumes per cent it was not due to acidosis. Reasoning that with fat necrosis neutral fat is split into fatty acids and glycerol, calcium could be removed to form soaps with fatty acids. Studies showed that the blood calcium may fall between the third and eleventh day. As much as 1,732 mg. of calcium may be present in two kilograms of the pancreas and adjacent fatty tissue. Lewison<sup>42</sup> found an incidence of pancreatitis of one in one thousand. In a study of blood amylase figures of 35 cases, he felt strongly that the blood enzymes were diagnostic. The rise in blood amylase must be sought for early as the elevation is only transient and disappears in a week. Rhodes<sup>43</sup> believes the blood amylase figures are of the greatest values early in the disease, but fluctuate widely and should be frequently repeated. He has made the observation and I have always believed that subsequent readings may be subnormal as the gland is increasingly destroyed. He also reserves surgery for those cases with supervening suppuration and not the acute, mildly, or severely ill patients. However, his specific reason is that a cholecystectomy does not drain the pancreas, except where a common channel exists, and this supposedly in a small number of cases. Popper and Plotke<sup>44</sup> studied blood amylase and lipase following intravenous injections of commercial trypsin containing large amounts of amylase and lipase. They also replaced 60 per cent of a dog's blood with that of another animal suffering from experimental acute pancreatitis. In another group, acetyl- $\beta$  methyleholine and eserine were injected and the blood enzymes estimated. The results were applied to acute pancreatitis in man. In a relatively slightly damaged pancreas the blood enzymes are eliminated rapidly. A high level over several days indicates a continued replacement of blood amylase and lipase and a severely active pathologic process.

Ephedrine and atropine should be used as medical treatment to stimulate the sympathetic nervous system and decrease the vagal secretion of the pancreas. A stomach tube will remove the normal physiologic stimulus. Kaufman and Calhoun<sup>45</sup> advise early surgery routinely. Of 41 cases, 28 were subjected to surgery with a 42 per cent mortality. Thirteen were given medical treatment, with a mortality of 38.4 per cent. Although the results of surgery were inferior, they feel it is definitely better as more seriously ill patients were operated upon. Cholecystostomy with later removal and drainage down to the pancreas is performed. If biliary tract pathology is found, a decompression is allowed. Directly opposed to this, Nordmann's<sup>46</sup> mortality dropped from 50 per cent to 24 per cent under conservative therapy. Mikkelsen<sup>47</sup>

of the common pancreatic duct may allow the ready mixing of bile, pancreatic juice, and duodenal contents in the pancreatic ducts. Archibald<sup>31</sup> is a strong proponent of the theory that spasm may cause reflux into the pancreatic duct. He had observed the ampulla to close immediately upon the application of acid or gauze. He also found that increased pressure in the gall bladder, caused by bile or saline solution, would close the ampulla with regurgitation into the pancreas. Indeed, the reverse is also true since Diamond and Siegel, and Colp and Doubilet<sup>32</sup> have found active pancreatic enzymes in the bile from common duct drainage. To prevent the spasm from operating, Archibald now cuts the sphincter through the duodenum. However, it would seem that the sphincterotome as used by Colp and Doubilet<sup>33</sup> might simplify this. Archibald, unable to demonstrate digestion of the pancreas by trypsin or trypsinogen in vivo or in vitro, objects to the bile-activated trypsinogen theory of acute pancreatitis. By injecting infected bile into the pancreatic duct in small quantities under very low pressure, he was able to produce intense edema of the pancreas with subsequent necrosis. Pancreatic tissue placed in bile showed the most rapid autolysis and digestion. Colp and Doubilet<sup>34</sup> have shown that infected bile has a greater content of bile salts and Flexner<sup>35</sup> has demonstrated that it is the bile salts which cause the most rapid necrosis of normal pancreas.

Smyth<sup>36</sup> has revealed the importance of the vascular factors. After injecting droplets of mercury into the arteries of the pancreas, typical areas of acute hemorrhagic pancreatitis developed in each animal. However, these were focal or multiple focal with no resemblance to the spreading type. Rich and Duff<sup>37</sup> subscribe to the vascular basis of acute pancreatitis. In their monumental work, they demonstrated that activated trypsin could cause the varying degrees of pancreatitis depending upon the amount liberated. Lyness<sup>38</sup> reported 18 cases of pancreatitis. Of these, 3 were due to vascular occlusion with massive necrosis and hemorrhage. Seven cases of diffuse and focal pancreatitis did not clearly demonstrate the clinical cause, but definitely suggested small vessel occlusion, duct obstruction, or local infection. The 8 that remained were obviously due to obstruction somewhere in the pancreas, though the exact site could be demonstrated in only 4. Lyness attributed the condition to duct-cell metaplasia with obstruction due to the heaping up of the epithelial cells. Many fine photomicrographs illustrate these nodules growing into the ducts.

The lymphangitis theory as expounded by Deaver and Sweet<sup>39</sup> is no longer supported though it gave a very facile explanation. A lymphatic route from the common duct to the head of the pancreas has not been demonstrated.

Popper and Necheles<sup>40</sup> found that the lymph, portal, and peripheral blood had the same amount of amylase and lipase in fasting dogs. Following the injection of 100 to 200 cat units of secretin there was a rise

6. Whipple, A. O., and Bauman, L.: *Am. J. M. Sc.* 201: 629-638, 1941.
7. Kennard, H. E.: *SURGERY* 9: 65-79, 1941.
8. Burtneiss, H. I., Koehler, A. E., and Saint, J. H.: *Ann. J. Int. Med.* 14: 1915-1932, 1941.
9. Fisher, N. F.: *Am. J. Physiol.* 67: 634-643, 1924.
10. Hershey, J. M.: *Am. J. Physiol.* 93: 637, 1930.
11. Best, C. H., and Huntsman, M. E.: *J. Physiol.* 75: 405, 1932.
12. Dragstedt, L. R.: *J. A. M. A.* 114: 29-32, 1940.
13. Mellenry, E. W., and Gavin, G.: *J. Biol. Chem.* 134: 683-692, 1940.
14. Montgomery, M. L., Skeline, G. E., and Chaikoff, I. L.: *Am. J. Physiol.* 131: 578-783, 1940-41.
15. Entenman, C., Chaikoff, I. L., and Montgomery, M. L.: *J. Biol. Chem.* 137: 699-706, 1941.
16. Entenman, C., and Chaikoff, I. L.: *J. Biol. Chem.* 138: 477-485, 1941.
17. Kauer, J. T., and Glenn, F.: *Am. J. Physiol.* 131: 437-440, 1940.
18. Cole, W. H., and Howe, J. S.: *SURGERY* 8: 19-33, 1940.
19. Council on Pharmacy and Chemistry of the American Medical Association: *J. A. M. A.* 115: 1454-1455, 1940.
20. Hammarsten, E., Agren, G., and Lagerlof, H.: *Acta med. Scandinav.* 92: 256-266, 1937.
21. Diamond, J. S., Siegel, S. A., Gall, M. B., and Karlen, S.: *Am. J. Digest. Dis.* 6: 366-372, 1939.
22. a. Diamond, J. S., Siegel, S. A., and Myerson, S.: *Am. J. Digest. Dis.* 7: 133-136, 1940.  
b. Diamond, J. S., and Siegel, S. A.: *Am. J. Digest. Dis.* 7: 435-442, 1940.  
c. Diamond, J. S., and Siegel, S. A.: *New York State J. Med.* 41: 869-874, 1941.
23. Tucker, H. F., and Ball, E. G.: *J. Biol. Chem.* 139: 71-80, 1941.
24. Ball, E. G., Tucker, H. F., Solomon, A. K., and Vennesland, B.: *J. Biol. Chem.* 140: 119-129, 1941.
25. Hug, E.: *Compt. rend. Soc. de biol.* 134: 163-164, 1940.
26. Thomas, J. E., and Crider, J. O.: *Am. J. Physiol.* 134: 656-663, 1941.
27. Comfort, M. W., and Osterberg, A. E.: *Arch. Int. Med.* 66: 688-706, 1940.
28. Bernard, Claude: *Lecons de physiol. experimentale appliquee a La Medicine*, Paris; 1855, J. B. Bailliere, vol. 2, p. 278.
29. Opie, E. L.: *Diseases of the Pancreas*, Ed. 1, Philadelphia, 1903, J. B. Lippincott Co.
30. Cameron, A. L., and Noble, J. F.: *J. A. M. A.* 82: 1410-1414, 1924.
31. Archibald, E.: *Proc. Inst. Med. Chicago* 13: 134-147, 1940.
32. Colp, R., and Doubilet, H.: *SURGERY* 4: 837-846, 1938.
33. Colp, R., and Doubilet, H.: *J. Mt. Sinai Hosp.* 7: 334-342, 1941.
34. Colp, R., and Doubilet, H.: *Arch. Surg.* 34: 149-173, 1937.
35. Flexner, J.: Quoted by Archibald.
36. Smyth, C. J.: *Arch. Path.* 30: 651-669, 1940.
37. Rich, A. R., and Duff, G. L.: *Bull. Johns Hopkins Hosp.* 58: 137, 1936.
38. Lynch, K. M.: *Ann. Int. Med.* 14: 628-640, 1940.
39. Deaver, J., and Sweet, J. E.: *J. A. M. A.* 77: 194, 1921.
40. Popper, J. L., and Necheles, H.: *Proc. Soc. Exper. Biol. & Med.* 43: 220, 1940.
41. Edmonson, H. A., and Fields, I. A.: *Proc. Soc. Exper. Biol. & Med.* 45: 803-804, 1940.
42. Lewison, E. F.: *Arch. Surg.* 41: 1008-1037, 1940.
43. Rhodes, G. K.: *West. J. Surg.* 49: 266, 1941.
44. Popper, H. L., and Plotke, F.: *SURGERY* 9: 706-711, 1941.
45. Kaufman, L. R., and Calhoun, E. J.: *New York M. Coll. & Flower Hosp. Bull.* 3: 185-190, 1940.
46. Nordmann, O.: *Arch. f. klin. Chir.* 193: 370-382, 1938.
47. Mikkelsen, O.: *Acta chir. Scandinav.* 75: 373-415, 1934.
48. Walters, W., and Cleveland, W. H.: *Arch. Surg.* 42: 819-838, 1941.
49. Slumacher, Jr., H. B.: *Ann. Surg.* 112: 177-200, 1940.

reported a 7.5 per cent mortality in 39 cases treated expectantly, although 50 per cent were acutely ill. However, cholecystostomy is still popular. I believe that it is most important not to remove the gall bladder as this may be urgently needed for anastomosis later.

Walters and Cleveland<sup>45</sup> find the only useful tests of pancreatic function are blood enzymes, lipase, and amylase, study of pancreatic ferments with or without secretin, and studies of the urine and stools.

#### ACUTE PANCREATITIS AND DIABETES

We are most prone to consider only the external secretory function of the pancreas in acute pancreatitis. While most of the pathology is localized in the ducts and acini of the pancreas, the islet cells are often more than temporarily damaged. Many mild diabetics are made worse and often this disease owes its inception to inflammation of the pancreas. Shumacher<sup>46</sup> in a series of 18 cases reported 27 per cent showing glycosuria during acute pancreatitis. A mild diabetic who suddenly, with little cause, developed a severe, intractable diabetic coma was found to have pancreatitis at autopsy. Lynch cites post-mortem results of a woman who had diabetes nine years previously with apparent recovery. Here was marked scarring of the pancreas, with obliteration of acini in some lobules, although ducts and islets were present in these areas. A patient whose case I had the opportunity to follow suffered a severe suppurative pancreatitis. The secretin test revealed the most marked diminution of pancreatic function I had seen. At no time was diabetes present during the year she was observed, though another mild attack of pancreatitis occurred.

#### CONCLUSIONS

1. A definite avenue for future progress has been indicated in surgery of the pancreas for hyperinsulinism.
2. The status of lipocaeic as a hormone has been evaluated, indicating it is still in the experimental stage.
3. The secretin test has definite value in the study and diagnosis of pancreatic disease.
4. Acute pancreatitis should be treated conservatively. The etiology of this disease remains controversial.
5. Diabetes has a definite relationship to inflammation of the pancreas and may be initiated by acute pancreatitis.

Grateful acknowledgment is extended to Dr. Frank Co-Tui for his kind assistance.

#### REFERENCES

1. Harris, S.: J. A. M. A. 83: 720, 1924.
2. Wilder, R. M., Allen, F. N., Power, M. H., and Robertson, H. E.: J. A. M. A. 89: 348, 1927.
3. Whipple, A. O., and Frantz, V. K.: Ann. Surg. 101: 1299-1335, 1935.
4. Whipple, A. O.: Chic. Surg. Soc., 1940.
5. David, V. C.: SURGERY 8: 212-224, 1940.

of laxity in one or the other of the sacroiliac joints. It requires that three films be taken centering over the symphysis pubis: One with the patient standing with weight equally distributed on both feet; one with the patient standing on the right foot alone, and finally on the left foot alone. In the presence of laxity of a sacroiliac joint, there will be a slight rise of the pubic bone on the affected side. The author felt that in a series of 144 cases studied, the technique had been most helpful in discovering the presence of this lesion.

Austin Moore, Columbia, S. C.: **Vitallium Replacement of Upper Two-Thirds of Femur, Following Nailing for Non-Union of Neck of Femur, Subsequent Bone Graft for Giant Cell Tumor and Finally Resection of Bone.**—This presentation was given in the form of a motion picture film. Because of the aggressive nature of the tumor in the trochanteric region of the femur, the author felt it was necessary to resect the entire upper third of the femur including the head and neck. This area of bone resected was replaced with a vitallium mold which was then attached to the distal femoral fragment. The technical details of the operative procedure were shown. The end result which depicted the patient walking on the extremity was startling indeed. The author pointed out several defects in the procedure discovered during the course of observation and suggested improvements which might be used to advantage in other similar cases. The successful replacement of such a large defect in a weight-bearing bone, with a vitallium mold, will certainly open a further field of reconstructive surgery.

H. Alvin Jones, Baltimore, Md.: **Congenital Synostosis of the Cervical Spine (Klippel-Feil Syndrome)**—A Study of Case Reports.—The author summarized the findings in some 31 cases studied. The nature and theories as to the etiology of the defect in the vertebral column were summarized briefly. He felt that the deformity resulting from its presence could be minimized by early recognition, prolonged physical therapy, and adequate brace support. Photographs of several cases treated in accordance with this plan were shown.

Major Leonard Peterson, U.S.A.: **Two Cases of Interscapulothoracic Amputation.**—The technique of an interscapulo-thoracic amputation was reviewed. The author then presented the case histories of two patients so treated at Walter Reed Hospital in Washington, D. C. The first case was that of a Ewing tumor involving the upper third of the humeral shaft. Early metastatic lesions in the lungs were reported. The second case, a patient with a fibrosarcoma of the shoulder girdle, was apparently successful in arresting progress of the lesion to date. A prosthesis had been furnished to compensate for the cosmetic deformity of the shoulder. End result photographs showing the patient dressed gave a very satisfactory impression.

William Rogers, Boston, Mass.: **The Treatment of Fracture and Dislocation of the Cervical Spine.**—The author advocates a radical departure from the usual method of treating fracture dislocation of the cervical spine. He feels that the results from previous conservative traction and prolonged immobilization have not always been satisfactory in preventing recurrence of the dislocation once support has been removed. Furthermore the length of recumbency can be appreciably shortened without danger if his regime is followed exactly. The essential steps in the proposed method of treatment are as follows: (a) The use of a mechanical Thomas collar for protection until an accurate x-ray examination has been made and studied. (b) Skeletal traction, the first step in actual treatment, is applied as quickly as x-rays are taken, to safeguard the cord and roots against further injury, and to pave the way for complete reduction. The usual measures are taken to minimize complications during the next several days.



# Review of Recent Meetings

---

## REVIEW OF THE MEETING OF THE AMERICAN ACADEMY OF ORTHOPEDIC SURGEONS, TENTH ANNUAL CONVENTION, ATLANTIC CITY, N. J., JANUARY 11-15, 1942

FRANK J. COX, M.D., NEW ORLEANS, LA.

*(From the Department of Surgery, School of Medicine, Tulane University)*

THE TENTH Annual Convention of the American Academy of Orthopedic Surgeons was held in Atlantic City, N. J., January 11 to 15. During this meeting an innovation was made in the general program, a series of instructional courses being given in various subjects related to the field of orthopedic surgery. Advance registration was required for attendance at these courses. Many favorable comments were made regarding their general excellence.

The scientific program was initiated January 12. The following presentations were given.

Edwin Weinberg, Baltimore, Md: **Two Cases of Late Rupture of the Extensor Pollicis Longus Tendon Following Colles' Fracture.**—A short review of the literature on this rare type of lesion was given. The rupture apparently occurs as a late complication. Its relationship to the original injury and the importance of early recognition and repair of the defect in the tendon were pointed out. Excellent results were obtained following delayed repair in the two cases presented.

O. A. Engh, Washington, D. C.: **The Steinman Pin in Fracture Fixation.**—The author presented a series of cases where Steinman pins were used widely to maintain position of the fracture fragments. The main emphasis was laid upon the insertion of the pins in an oblique direction, and then incorporation of the pins in plaster. By this means more rigid fixation at the fracture site was assured, and the possibility of rotation about the pins, or motion between the skin and the plaster edge minimized. A series of illustrative cases showing the results of the method as used by the author were presented. On the whole the results appeared satisfactory.

Lieutenant Commander Robert Mazet, Jr., USN: **A Report of Thirty Cases of Osteochondritis Desiccans.**—The various theories advanced to explain the etiology of this condition were discussed briefly. It was pointed out that even though trauma commonly caused the initiation of symptoms, it probably was not always the direct cause of the lesion. The majority of the cases shown were localized in the knee joint. The advantage of injection of air into the knee joint to localize a loose body more accurately was brought out in one case quite clearly. Uniformly good results were obtained in all cases following excision of the fragmented area of bone.

Randolph L. Anderson, Charleston, W. Va.: **The Clinical Use of the Chamberlain Technique in Back Examinations.**—The Chamberlain technique of x-ray examination in the study of low back pain is designed to discover the presence

his own method of repairing a recurrent dislocation of the shoulder was equally satisfactory and technically a much easier operation than Bankhart's procedure.

**William T. Green, and Sidney Ferber, Boston, Mass.: Eosinophilic or Solitary Granuloma—Is It a New Disease?**—The authors presented their findings in a series of 12 cases followed over a period of years. The disease process was uniformly characterized by localized destructive lesions of bone which were either single or multiple. In the single lesions, the defect seen on x-ray was identical with that of solitary bone cyst. In the multiple lesions, the distribution and roentgen appearance resembled that of metastatic malignancy or myeloma. One case showed twenty-six areas of involvement of the skeleton. The disease in all cases was limited almost completely to a destructive lesion in the skeletal system with no reactionary bone formation.

Careful clinical observations and biopsies were made in all instances. The lesions seemed to conform to the picture recently described as a new disease, "solitary granuloma of bone." The authors presented as their opinion, that this process was actually a variation of the same basic disease represented by Schüller-Christian's or Letterer-Siwe's disease. A most interesting scientific exhibit was shown to substantiate their conclusions further.

**Robert L. Carroll, Los Angeles, Calif.: The Rate and Amount of Increase in Muscle Strength Following Infantile Paralysis.**—A study of early and late after-effects of infantile paralysis in 1500 cases was made under a grant from the National Foundation for Infantile Paralysis. In judging the degree of residual paralysis Dr. Lowman's scale of 0-9 was used throughout this study. By means of statistical analyses an effort was made to determine the general pattern of return in muscle strength. The conclusion reached was that the greatest increase was found in the first six months after onset of illness, the average degrees of improvement representing three points on the Lowman scale. During the period from six months to ten years after onset, approximately one point more increase in muscle strength was gained. Though most of these patients did receive prolonged physiotherapy, no conclusion was drawn by the author as to the efficacy of these measures in promoting more rapid or complete return of power in any case.

**Mather Cleveland, and David M. Bosworth, New York, N. Y.: A Study of Gross and Microscopic Lesions in Tuberculosis of the Spine.**—The authors showed an extremely interesting scientific exhibit in conjunction with this presentation. They had collected a series of proved cases of tuberculosis of the spine with pre-operative roentgenograms, gross specimens obtained at autopsy, and films taken of the gross specimens after removal from the body. Following careful study of this material they felt they could state definitely that tuberculosis of the spine always appeared in one of two fashions: (a) as a process of caseation and necrosis in the body of the vertebra itself, the result of local emboli of tubercle bacilli, or (b) as an area of sclerosis in the body due to interference with the blood supply to this area which interference in turn could be attributed to stripping of the soft tissues from its surface by a spreading abscess. Since there were no vessels entering the intervertebral disk they felt that it was impossible for an embolus to reach this point, hence the opinion that narrowing of the intervertebral space represented one of the early signs of tuberculosis of the spine was erroneous. When involvement of the disk appears the process is already widely established in the adjacent soft tissues and probably vertebral bodies also. The earliest signs of embolic phenomena in the bodies of the vertebrae were therefore due to the resultant caseation and local necrosis which when viewed on the roentgenogram appeared as areas of mottling. When the

As soon as the patient's general condition will warrant (c) an open operation is done and the reduction completed. (d) Internal fixation of the dislocation is assured by the use of an autogenous bone graft secured with wire. (e) When wound healing is complete an ambulatory brace is fitted and worn. The author feels this method is quite as efficient as the older type of prolonged plaster fixation, particularly since the graft is firmly fixed in situ. A series of cases so treated were reviewed.

**Rudolph S. Releh, Cleveland, Ohio: Treatment of Flexion Deformities of the Knee.**—The author reviewed briefly the various causes leading to the development of a flexion deformity of the knee joint, and voiced a plea for more widespread dissemination of knowledge as to the necessity of preventing their occurrence. He emphasized the point that the majority of these deformities can be easily avoided if proper splinting is furnished the patient during the acute stages of their illness. When the contracture had become fixed and there was no contraindication to surgical correction, the author felt that his method of correction had proved valuable. He advised exposure of the posterior aspect of the thigh and popliteal space through two incisions, one over the biceps tendon laterally, and the second along the lateral edge of the semimembranosus tendon. Through the lateral incision the tendon of the biceps femoris muscle is isolated and a Z type lengthening done. Through the medial incision the internal hamstring are lengthened and a check made on the degree of extension obtained. If further correction is needed the origin of the gastrocnemius is stripped loose from the femur. As a final measure only, is posterior capsulotomy of the knee joint advocated. The author stressed the fact that with this type of exposure a better view of the posterior portion of the knee could be obtained, and a more rational attack made upon the various factors causing the contracture to persist.

**Frederic C. Bost, and Verne Inman, San Francisco, Calif.: Pathology of Recurrent Dislocation of the Shoulder: Report of Bankhart's Operative Procedure**—In July, 1938, Bankhart reported the pathology of recurrent dislocation of the shoulder as proved by him in 27 consecutive cases. The lesion consisted of a tear of the glenoid labrum and the repair of the dislocation was effected by reattachment of the glenoid labrum.

The authors report verification of Bankhart's findings, based upon anatomic studies, and clinical observations in 10 cases operated upon for recurrent dislocation of the shoulder and repaired according to Bankhart's technique. They pointed out the fact that the presence of a defect in the glenoid labrum could be demonstrated in several of their cases by x-ray views taken in a tangential plane. The difficulty encountered in obtaining exposure of the glenoid labrum at the time of operation was pointed out as constituting one undesirable feature of this particular type of repair.

**Toufiek Nicola, Montclair, N. J.,** in his discussion of this paper described a series of experiments done by him on cadavers attempting to reproduce a dislocation of the humeral head. His conclusions were two: (a) If the humerus is merely abducted, then, as it impinges against the acromion and the force is continued, the capsule of the shoulder joint tears loose from the humerus or the neck of the scapula. (b) If, however, in addition to the abduction force, an impaction force is applied the capsule tears from the glenoid labrum. In four cases of acute dislocation of the shoulder explored at operation, these experimental findings were corroborated. He felt that any dislocation of the shoulder associated with a defect in the glenoid labrum would predispose toward a recurrent dislocation of the shoulder, that one associated with a tear of the capsule from the humerus or neck of the scapula would not do so. The author felt that

The clinical impressions of the author were corroborated by similar observations reported by Alan Deforest Smith of New York City, Edward L. Compere of Chicago, and Walter Blount of Milwaukee

Philip Lewin, and Louis Scheman, Chicago, Ill: **Experimental Osteomyelitis.** The authors presented a preliminary report on the experimental production of a lesion simulating human osteomyelitis. They have used a broth culture of *Staphylococcus aureus* originally obtained from a patient with hematogenous osteomyelitis and subsequently passed through many rabbits. In the early work rabbits were used exclusively as experimental animals. The technique which proved successful was as follows: The animals received an immunizing subcutaneous injection and then were allowed to incubate for one week. At the expiration of this period 0.5 cc. of sodium morrhuate were injected into one of the tibial metaphyses, followed in one hour by 0.2 cc. of 1:50 dilution of a twenty-four-hour broth culture of *Staph aureus* into the same metaphysis. A lesion very closely simulating the disease as encountered in the human being was universally produced. Roentgenograms, cultures, and microscopic examinations were made to prove this point. In the later stages of the experimental work identical results were obtained on dogs. This contribution opens a wide field for further experimental work on osteomyelitis, both chronic and acute. For years attempts have been made to reproduce in animals lesions in bone resembling human osteomyelitis, always with questionable success. The authors presented their technique as a uniformly successful method for experimental production of this disease, and suggested a few of the wide problems it may open for further investigation.

Alan Deforest Smith, and Lawson E. Miller, New York, N. Y. **The Value of Laminograph in the Treatment of Chronic Osteomyelitis.** A short series of cases of chronic osteomyelitis were discussed, the histories reviewed, and x-rays shown, in which accurate localization of the offending focus in the shaft was masked in the ordinary roentgenogram. By means of the laminograph, it is possible to locate and treat these areas with accuracy. A radiopaque substance was injected into the open sinuses to substantiate the findings further. This appears to be a valuable adjunct to the treatment of obscure cases of osteomyelitis, when the apparatus is available for use.

Lenox D. Baker, Durham, N. C.: **The Report of the Use of Sulfonamides in Traumatic and Infected Wounds.**—An effort was made by the author to evaluate the true efficacy of the sulfonamides when used locally and systemically to control infection in the extremities. The work was made possible through a series of case reports made by various members of the Academy throughout the country. In the present report three classifications were used: (1) Chronic osteomyelitis (Table I); (2) Old compound fractures with infection (Table II); and (3) Fresh compound fractures (Table III).

TABLE I  
CHRONIC OSTEOMYELITIS

	TOTAL	HEALED	INFECTED
Surgery plus chemotherapy	74	54	20
Sulfanilamide	11	7	4
Primary closure	4	4	0
Open method	7	3	4
Sulfathiazole	63	47	16
Primary closure	41	36	5
Open method	22	11	11

disease process involved the soft tissues predominantly and the sole bone changes were due to stripping of the soft tissues from the body of the vertebra, then the resultant sclerosis would appear as a local area of increased density. If spread of the latter process was to be kept to a minimum, frequent aspiration of the abscess would be a very worthwhile procedure. They have proved it to be so in a group of active cases of spine tuberculosis followed at Seaview Hospital. The detection of these early bone changes by means of x-ray examination is most difficult, at times impossible. The authors feel, therefore, that when spino fusion is attempted a much wider area of fusion should be secured than has heretofore been considered adequate.

**J. B. Weaver, Kansas City, Mo.: Calcification and Ossification of Semi-Lunar Cartilages.** The author presented a brief review of the literature published on this subject to date, quoting 76 cases from the literature and adding two additional cases of his own. The typical changes occurring in the cartilage were segregated into two main types, primary and secondary. In the primary form, the lesions appeared as a generalized calcification in all the menisci. The patient is usually over 40 years of age. The etiology of this condition is not clear. Conservative therapy seems best suited. The secondary form involves a single meniscus only. The patient is usually under 40 years of age. A localized zone of calcification in a single meniscus occurs. This may or may not be completely apparent upon x-ray examination. The presence of the lesion leads to synovial changes, pain, swelling and loss of motion. Excision of the involved meniscus usually leads to a complete restoration of function. The etiology can frequently be attributed to trauma.

**Wallace H. Cole, St. Paul, Minn.: Further Report on the Kenny Treatment of Infantile Paralysis.** Fifty-one cases had been carefully studied up to Dec. 1, 1941. The author stated that in his opinion the results obtained had been most satisfactory, since he had noted these patients were much more comfortable during the acute stage of their illness, and that contractures and stiffness were universally prevented. The Kenny treatment is designed to combat three essential factors considered to be present in the involved musculature. These are in Sister Kenny's opinion: (a) incoordination of muscle action, which may be present within the muscle itself, or which may be the result of a secondary spread of impulses by reflex means from adjacent involved musculature, (b) disorientation in local muscle action manifested by the inability of the patient to produce a contraction even though the motor pathways to that muscle are unimpaired, and (c) muscle spasm which is considered the cause of local pain, fibrillary twitching, etc.

Active treatment is instituted as early as possible following onset of the disease. No splints are used. The feet are supported against a foot board in the "standing position," the arms allowed to lie free by the sides. Hot fomentations are applied over the involved musculature, leaving the joints exposed as much as possible. In the average case these hot moist packs are changed every two hours during a twelve-hour period, none being used during the night. In the more severe type of infection they are changed more frequently, even every fifteen minutes. Controlled passive motion is instituted early, through a range of motion which is not associated with pain. Incoordination and disorientation are combated from the start by personal supervision and education of the patient to acquire a mental attitude of cooperation in producing motion either passively or actively. This latter phase of the treatment is considered essential by Sister Kenny. Its proper conduct will require an accurate knowledge of individual muscle action and body mechanics, as well as a personality sufficiently developed to acquire the full confidence of, and cooperation from, the patient.

tion of all associated injuries was kept. The importance of careful examination was emphasized, since many associated injuries may be more serious in nature than the cerebral damage. A plea was voiced to avoid too energetic methods of examination and treatment of associated injury, in order to avoid unnecessary increase in the degree of intracranial damage and consequent rise in the mortality rate. A very careful regime of observation and treatment of primary skull fracture was presented, which when followed in detail gave definitely superior results. This consisted of intelligent management of the skull fracture and brain injury first, with the simplest type of temporary treatment of the associated injury, followed by intelligent management of the latter when the patient's condition warranted. A detailed review of this vast amount of material cannot be given properly in synopsis form. A careful study of the original article when published is strongly advised.

Charles F. Thompson, Indianapolis, Ind.: **Fusion of the Metacarpal of the Thumb and Index Finger to Maintain Functional Position of the Thumb.**—After the method of Allen in Birmingham, England, in which a keystone block of tibial cortex is used to fuse the metacarpal of the thumb to that of the index finger, maintaining the fixed rotation of the thumb in opposition to the fingers, the function of the so-called "paddle hand" may be markedly improved. The author presented a series of cases in which satisfactory results had been obtained with this method. The procedure is reserved for those cases where tendon transplant is not considered possible, and to those which show satisfactory grasping power. The same technique has proved of definite value in certain types of spastic paralysis. The procedure admittedly has a limited field of usefulness, but when indicated seems a most satisfactory answer to a difficult problem.

John H. Kuhns, Boston, Mass.: **The Orthopedic Treatment of Hypertrophic Arthritis of the Hip.**—The nonoperative procedures used for treatment of hypertrophic arthritis of the hip were discussed. One hundred and eighty-three patients were reviewed, 86 men and 97 women, who had been discharged from the hospital a year or longer. In 114 patients both hips were involved and in 69 one hip only was involved. Nonoperative treatment consists chiefly in attempts to remove mechanical factors which tend to make the condition worse. Chief among these is the increased forward inclination which comes with faulty body mechanics and increases with flexion deformity at the hip joint. This brings weight thrust upon the posterior part of the acetabulum rather than upon the strong and superior portion. In addition, muscular pulls are changed and muscular atrophy develops. Strain, fatigue and instability are the natural sequelae.

Treatment is directed primarily to bring weight bearing as nearly as possible upon the strong superior portion of the acetabulum. In addition such factors as obesity, endocrine disturbances and hygienic errors are corrected, if possible. A special pelvic belt is frequently necessary when the patients first become ambulatory. With special treatment complete relief of symptoms and ability to continue with their regular activities was observed in 29.7 per cent of the patients and partial relief in 36.8 per cent of the patients. Nonoperative treatment was least effective in young individuals with unilateral involvement and severe deformations of the femoral head. In addition to these measures for those who showed no improvement, manipulation of the hip was undertaken in eight instances, with marked improvement in deformity and in motion in seven. This procedure was of value where there was not much deformation of the femoral head. Roentgen therapy is a helpful measure for the relief of pain. It produces no other effect so far as could be determined. Relief of pain was observed after the use of roentgen therapy in 16 of 21 patients.

The results from the use of the sulfonamides, particularly sulfathiazole, in chronic osteomyelitis, according to the method of Dickson and Diveley, seemed most encouraging.

TABLE II  
OLD COMPOUND FRACTURE WITH INFECTION

	TOTAL	HEALED	INFECTED
Open reduction plus chemotherapy	47	30	17
Sulfanilamide	14	7	7
Primary closure	7	5	2
Open method	7	2	5
Sulfathiazole	33	23	10
Primary closure	20	17	3
Open method	13	6	7

In this group, particularly those cases treated according to the technique advocated by Dickson and Diveley, similar encouraging results were obtained.

TABLE III  
FRESH COMPOUND FRACTURES

	TOTAL	HEALED	INFECTED
Open reduction plus chemotherapy	270	217	53
Sulfanilamide	242	192	50
Sulfathiazole	28	25	3
Primary closure	252	205	47
Open method	14	11	3
Drained	4	1	3
Internal fixation	126	90	36

In an analysis of this group the author felt that he could not attribute any great value to the use of the drug locally, except to state that it did not cause any increase in the percentage of infections in compound fractures. Proper surgical technique and wound hygiene still appeared to be the major factors in controlling the amount and degree of infection in compound fractures.

The report on the whole is interesting but still not conclusive. It should be carried further and a longer follow-up made on groups (1) and (2).

Stuart A. Thomson, Toronto, Can.: **Treatment of Club Feet with Dennis-Browne Splints.**—The method used by the author is really a modification of original method as outlined by Dennis-Browne. Small malleable foot splints are used and the baby's foot strapped snugly to these with adhesive tape. The cross-bar is adjusted first to correct the forefoot adduction, then the varus of the heel, and finally the equinus deformity in order. The whole correction is obtained gradually, the force used being the force exerted by the baby in kicking. Primary correction is obtained during the first several weeks, and correction maintained for six to seven months in the metal plate and adhesive strapping. Boot-splints are fitted at the expiration of this time, and worn till the walking age is reached. A night-splint is used for the first two to three years, though free walking in a corrective shoe is encouraged from the start. The method is obviously of value in the very young infant group only, and has no place in any other group. An interesting motion picture showing end results of cases so treated was displayed.

Harry E. Moek, Chicago, Ill.: **The Management of Associated Injuries in the Presence of Skull Fracture.**—This report is based upon a nation-wide survey of 3,106 cases of skull fracture collected from nineteen hospitals. A careful tabula-

# SURGERY

VOL. 11

JUNE, 1942

No. 6

## Original Communications

### LUDWIG'S ANGINA

#### AN ANALYSIS OF FORTY-FIVE CASES

MAX TAPPEL, M.D., AND SAMUEL C. HARVEY, M.D., NEW HAVEN, CONN.

(From the Department of Surgery, Yale University School of Medicine)

**W**ILHELM FRIEDRICH VON LUDWIG,<sup>4, 15</sup> in 1836, published a report of the disease which now bears his name. A large number of communications on the subject have since appeared in the literature of all languages. Some of these communications have dealt with the etiologic bacterial agents involved. Others have attempted to disclose the exact pathogenesis and spread of the infection. Most have referred to the importance of having an exact knowledge of the anatomic structures in the neck and the floor of the mouth. All, however, have agreed that the disease is very serious and often fatal. The cause for the mortality has been attributed largely to some peculiar and cryptic virulence of the infecting organisms which rapidly overwhelms the patient and leads to his death, often a very sudden one. In 1908, in a detailed and admirable discussion of the subject, Thomas<sup>21</sup> pointed out that the majority of the deaths were due not to sepsis but rather to a mechanical respiratory obstruction. He related this obstruction directly to the narrow and unyielding boundaries within which the infection is tensely confined. He advised early operation for the relief of tension in the involved space, and recommended that the operation be performed under local anesthesia. The mortality rate in many series<sup>1, 2, 8, 21, 22, 23, 25</sup> has continued, nevertheless, to lie between the high brackets of 25 and 54 per cent.

It is not our purpose to enter here into involved and scholastic disputations relating to the exact points of origin of the infection, its spread by fascial spaces or lymphatics, or its primary or secondary nature. We do not mean to minimize the importance of these considerations in the study of the disease, but they do not happen to concern our present primary purpose. We wish, rather, to devote ourselves to the

Presented at the meeting of the Society of University Surgeons, Cincinnati, Ohio, Feb. 12-14, 1942.



Ralph K. Ghormley, and M. B. Coventry, Rochester, Minn.: **Surgical Treatment of Painful Hips in Adults.**—This review covered the cases of painful hips of adults that have been treated by surgery in the Mayo Clinic during the years 1938, 1939, and 1940. These included all types of painful hips, mostly, of course, hypertrophic arthritis.

Such procedures as arthroplasty with vitallium cup, arthrodesis, acetabuloplasty, and drilling operations were used for the most part. The results from these procedures were given. The arthrodesis, of course, was the most certain way of relieving pain; however, with the cup arthroplasty, which was performed in 13 cases, they were able to get improvement in motion in 11 of the cases and improvement from the standpoint of pain in 9 of the cases. In 9 of the 15 cases in which acetabuloplasty was carried out improvement was noted in regard to the relief of pain and amount of motion. With drilling, which was done in 8 cases, there was improvement from the standpoint of pain in 4 cases and from the standpoint of motion in 2 cases. Simultaneous review of the cases not treated by surgery in the same interval convinced the authors that surgical procedures do offer a considerable amount of relief to this group of patients

of that infection. The anatomic structures limiting these areas, the so-called submandibular space,<sup>10, 11, 12</sup> have been adequately described by others.<sup>1, 3, 6, 10, 11, 12, 21, 23</sup> No attempt will be made, therefore, to repeat these descriptions. An infectious process, whether associated with supuration or with edema alone, will increase the tension within this space and will displace the only yielding bordering structures, namely, the floor of the mouth, the tongue, and the pharynx. It is this displacement which is in a large measure responsible for the respiratory difficulties so characteristic of the disease. The edematous tongue is often

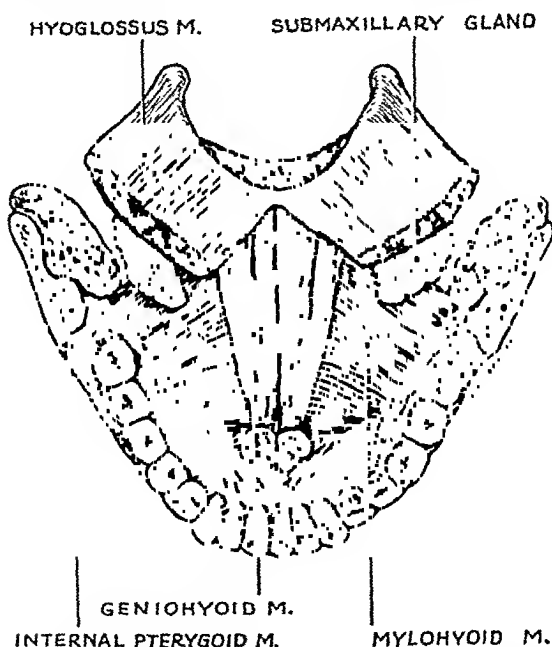


Fig. 2.—Diagrammatic sketch showing the diaphragm formed by the structures in the floor of the mouth. (From Christopher, Frederick: *A Textbook of Surgery*, W. B. Saunders Company.)

elevated to such an extent that the oral and pharyngeal cavities are almost completely filled. The displaced pharynx carries the epiglottis and larynx with it, and thus there is further encroachment upon an already seriously compromised airway. Because of its close proximity to the site of infection and because also of adjacent venous obstruction, the larynx itself may suddenly be involved in a rapidly progressive edema and become completely obstructed. Since the infection lies deep to the mylohyoid muscle and the cervical fascia, the skin of the neck in the submandibular and submaxillary areas will not be involved early in the disease and will slide freely over the underlying swollen and indurated tissues. Similarly, fluctuation is not an early sign and is almost invariably absent in the initial stages of the illness. Often no pus is present and the local distortion of the tissues is caused only by edema

task of dispelling the myth, still prevalent in many quarters, that Ludwig's angina is a sinister affliction endowed with some sort of mysterious and unalterably fatal sting. We wish to emphasize that when the disease is recognized early and is treated promptly and judiciously, the mortality rate will drop precipitantly. We shall support our contentions by an analysis of the cases treated at the New Haven Hospital over a period of twenty years.

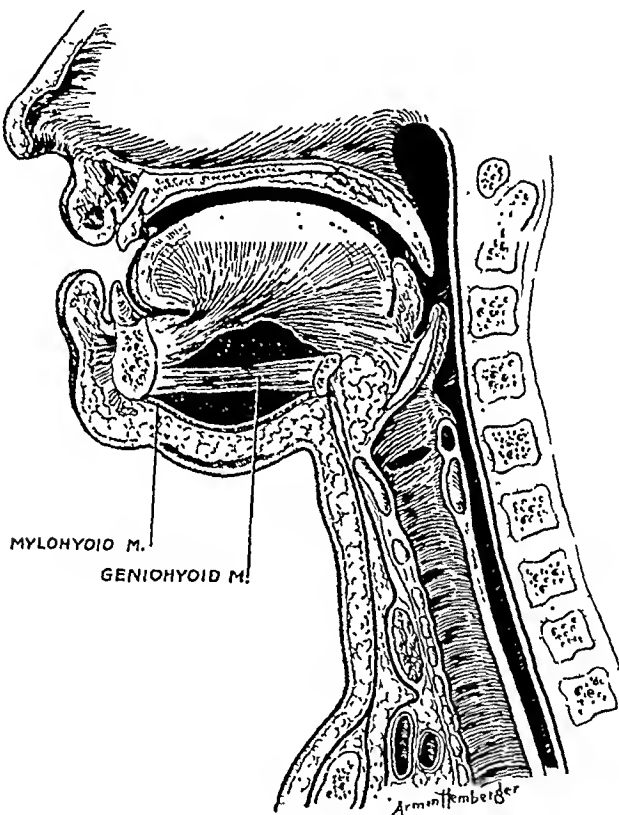


FIG. 1.—Diagrammatic sketch showing the location of pus in the submandibular space. (From Christopher, Frederick: *A Textbook of Surgery*, W B Saunders Company.)

#### CRITERIA FOR MAKING THE DIAGNOSIS

There has been a good deal of discussion as to what really constitutes Ludwig's angina. The term has often been loosely applied to any infection in the upper part of the neck, especially when it is associated with a brawny nonsuppurative induration and when it appears to be of a violent nature. We have included in our series only those infectious processes located in the areas between the mylohyoid and the geniohyoid, or between the geniohyoid and the genioglossus muscles (Figs. 1 and 2) regardless of the etiology, the point of origin, or the pathway of spread

complained of dyspnea. Some of the others who did not have dyspnea were hoarse. Trismus was present in more than one-half of the instances where it had been specifically mentioned.

*Interval Between Admission to Hospital and Operation.*—Thirty-two patients were operated upon immediately after admission, six on the first day, five on the second day, and three on the fourth day.

*Operation.*—Forty-six operations were performed in forty-three patients. The surgeons included many different members of the house and attending staffs. In three of the patients there was a subsequent spread of a unilateral infection to the opposite side which required, in each instance, a second operation. The remaining forty were each operated upon once. In two patients the infection subsided without operation, after spontaneous rupture of an abscess through the floor of the mouth.

*Anesthesia.*—Local novocain infiltration anesthesia was employed in forty-two operations. General inhalation anesthesia was used four times, once in a child five years old, once in a child seven years old, and twice in the same adult.

*Operative Findings.*—Frank pus (few drops to many cubic centimeters) was drained in thirty-five of the operations. Edema alone but no pus was found in eleven instances.

*Bacteriologic Findings.*—The majority of the cultures revealed the presence of more than one organism in the pus. The combinations were multiple and varied. The organisms were of the usual variety commonly found in any series of ordinary abscesses and included hemolytic streptococcus, nonhemolytic streptococcus, *Streptococcus viridans*, *Staphylococcus aureus*, *Staphylococcus albus*, spirochaetes and fusiform bacilli, *Haemophilus influenzae*, *Bacillus coli*, and diphtheroids. In the group where only edema was present the wound culture was sterile in four instances, *Staph. aureus* was cultured in two, *Staph. albus* in one, and spirochaetes and fusiform bacilli in one. In the remaining three cases the results of the cultures were not recorded.

*Course After Operation.*—In the survivals there was an immediate relief of symptoms following the operative procedure. The edema of the floor of the mouth and the elevation of the tongue rapidly subsided. The temperature and pulse fell to normal limits after about seven days. The wounds healed after draining for a period of several weeks.

*Mortality.*—There were two deaths. Autopsies were performed in both fatal cases. One had a dissecting aortic aneurysm which had suddenly ruptured into the thorax. The other had a concomitant suppurative cavernous sinus thrombophlebitis, lung abscess, and pneumonia.

*Tracheotomy.*—Tracheotomy was performed three times: in one patient as an emergency procedure immediately after admission to the hospital and while en route to the operating room; in the second patient, six hours after an inadequate operation had been performed; in the third patient, twelve hours after an adequate operation.

associated with the cellulitis. However, even when present, the pus is so deep and so tensely confined that the characteristic sign of fluctuation cannot be elicited. The earliest and therefore the most important clinical manifestations of an infection within the submandibular space, and the ones which we have used as criteria for making the diagnosis of Ludwig's angina are: (1) a deep and tender swelling in the submaxillary and submandibular areas of the neck; (2) swelling of the floor of the mouth; (3) elevation of the tongue. The systemic manifestations are generally the same as those in any other infectious process of similar nature and extent. The clinical diagnosis was verified by operation in forty-three of our cases, and in the remaining two by a spontaneous rupture of the abscess through the mucous membrane of the floor of the mouth. Dysphagia, hoarseness, dyspnea, pneumonia, and septicemia are all later arrivals, and one should not wait for them before recognizing the true nature of the disease.

#### ANALYSIS OF CASES

Forty-five patients were treated for Ludwig's angina at the New Haven Hospital between the years 1922 and 1941 inclusive. There were thirty males and fifteen females. The ages varied from 5 to 67 years. There were two in the first decade of life, eleven in the second, twelve in the third, six in the fourth, eight in the fifth, two in the sixth and four in the seventh.

*Antecedent Factors.*—Infected teeth were responsible for the onset of the disease in thirty-one cases. In nineteen there was a history of a recent lower molar tooth extraction. Twelve patients had complained of lower molar toothache. Apical abscesses were subsequently revealed in some of these by x-ray examination. There were two instances of trauma to the floor of the mouth by foreign bodies, glass in one and a wisp of hay in the other. Two patients had had a previous submaxillary adenitis, two had compound fractures of the mandible, four had "sore throats," and one had lupus erythematosus with multiple mucous membrane lesions. In three cases no antecedent cause of any kind could be discovered.

*Duration of Symptoms Before Admission to the Hospital.*—This period varied from 18 hours to seven days, the average being about three days.

*Signs and Symptoms.*—All the patients were ill and presented themselves on admission with sharp and significant rises in temperature, pulse, and blood leucocyte count. All complained of a painful swelling in the submaxillary and submandibular areas of the neck. Swelling of the floor of the mouth and elevation of the tongue were present in forty-four cases. The remaining patient had such severe trismus that the mouth could not be opened sufficiently for adequate examination. Dysphagia was recorded in forty-one instances. Thirteen of the patients

complained of dyspnea. Some of the others who did not have dyspnea were hoarse. Trismus was present in more than one-half of the instances where it had been specifically mentioned.

*Interval Between Admission to Hospital and Operation.*—Thirty-two patients were operated upon immediately after admission, six on the first day, five on the second day, and three on the fourth day.

*Operation.*—Forty-six operations were performed in forty-three patients. The surgeons included many different members of the house and attending staffs. In three of the patients there was a subsequent spread of a unilateral infection to the opposite side which required, in each instance, a second operation. The remaining forty were each operated upon once. In two patients the infection subsided without operation, after spontaneous rupture of an abscess through the floor of the mouth.

*Anesthesia.*—Local novocain infiltration anesthesia was employed in forty-two operations. General inhalation anesthesia was used four times, once in a child five years old, once in a child seven years old, and twice in the same adult.

*Operative Findings.*—Frank pus (few drops to many cubic centimeters) was drained in thirty-five of the operations. Edema alone but no pus was found in eleven instances.

*Bacteriologic Findings.*—The majority of the cultures revealed the presence of more than one organism in the pus. The combinations were multiple and varied. The organisms were of the usual variety commonly found in any series of ordinary abscesses and included hemolytic streptococcus, nonhemolytic streptococcus, *Streptococcus viridans*, *Staphylococcus aureus*, *Staphylococcus albus*, spirochaetes and fusiform bacilli, *Haemophilus influenzae*, *Bacillus coli*, and diphtheroids. In the group where only edema was present the wound culture was sterile in four instances, *Staph. aureus* was cultured in two, *Staph. albus* in one, and spirochaetes and fusiform bacilli in one. In the remaining three cases the results of the cultures were not recorded.

*Course After Operation.*—In the survivals there was an immediate relief of symptoms following the operative procedure. The edema of the floor of the mouth and the elevation of the tongue rapidly subsided. The temperature and pulse fell to normal limits after about seven days. The wounds healed after draining for a period of several weeks.

*Mortality.*—There were two deaths. Autopsies were performed in both fatal cases. One had a dissecting aortic aneurysm which had suddenly ruptured into the thorax. The other had a concomitant suppurative cavernous sinus thrombophlebitis, lung abscess, and pneumonia.

*Tracheotomy.*—Tracheotomy was performed three times: in one patient as an emergency procedure immediately after admission to the hospital and while en route to the operating room; in the second patient, six hours after an inadequate operation had been performed; in the third patient, twelve hours after an adequate operation.

*Complications.*—Pneumonia, lung abscess, and cavernous sinus thrombophlebitis were present once. All occurred in the same patient. It is probable that the pneumonia and lung abscess were complications of the cavernous sinus thrombophlebitis rather than of the Ludwig's angina. It is probable also that the cavernous sinus thrombophlebitis was a coeval infection and did not originate from the angina. There were no instances of mediastinitis.

#### SUMMARY AND DISCUSSION

Ludwig's angina is a disease which is attended with a constant threat to the life line of the upper air passages and which therefore demands immediate emergency treatment. Fortunately, there are distinctive clinical manifestations which appear very early in the disease and can be easily recognized. The local diagnostic criteria are an external tender swelling beneath the mandible, swelling of the floor of the mouth, and elevation of the tongue. The onset of total respiratory obstruction is often exceedingly sudden and dramatic. The patient may fail to complain of any appreciable respiratory embarrassment. Indeed he may not become aware of its existence until the obstruction is on the verge of becoming complete. This obstruction is caused largely by a distortion and displacement of the tongue and pharynx which are in turn the result of tension within the submandibular space. In addition, there may be a concomitant edema of the larynx. The primary object, therefore, is not merely to drain pus, but rather to decompress the submandibular space and to release the tension within it as early and as completely as possible. This can be accomplished with certainty only by transverse section of the deep fascia and the mylohyoid muscle on one or both sides, depending upon whether the infection is unilateral or bilateral. Our operative procedure consists of making an incision in the skin and platysma beneath and parallel to the horizontal ramus of the mandible. The incision is deepened to include the deep fascia, the anterior belly of the digastric muscle, and the mylohyoid muscle, all of which are divided transversely and completely. If it is suspected that the infection lies above the geniohyoid, that muscle too is divided. The floor of the submandibular space is thus laid open and the tension within it is fully released. This allows the tongue and floor of the mouth to fall back into more normal positions. The local venous engorgement is also to a large extent relieved. A division of the fibers of the mylohyoid muscle should be thorough and total, regardless of whether actual pus or edema is present. It should further be emphasized that this muscle should be transected even when pus is encountered immediately under the skin and platysma. The subcutaneous pus often communicates with the submandibular space through a narrow and tortuous tunnel. The drainage of this pus alone may therefore not appreciably change the degree of tension within the main submandibular pocket. In one of our cases the

operative procedure was terminated after the simple drainage of such a subcutaneous abscess. The respiratory difficulty was not relieved and an emergency tracheotomy had to be performed six hours after the operation. The skin incision should be planned so as to avoid injuring the mandibular branch of the facial nerve, and so that the final scar will come to lie under the chin, where it will not be conspicuous. An incision midway between the hyoid bone and the lower border of the mandible will usually meet these two objectives. For bilateral infection, a horse-shoe shaped incision is made at the same level (Fig. 3). This incision, unilateral or bilateral, allows a more thorough exploration and decompression, and is attended in general with a finer cosmetic result than the midline vertical incision. The whole wound is left open and a

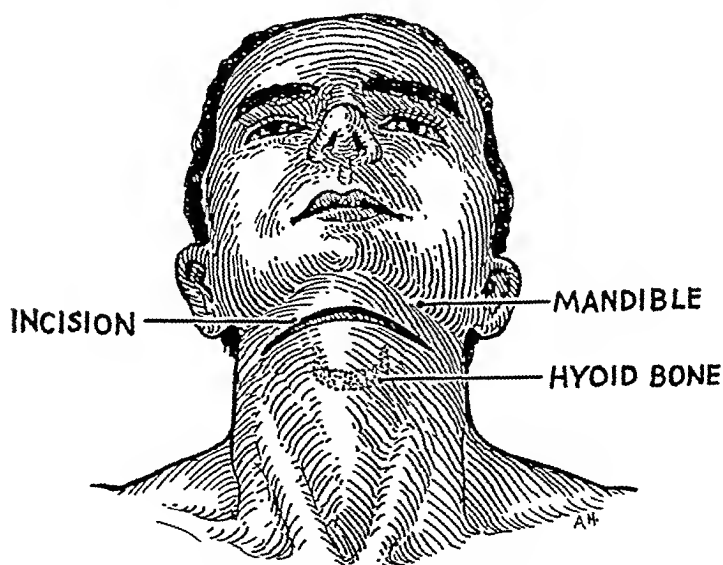


FIG 3.—Diagrammatic sketch showing site of operative incision.

vaseline gauze pack is placed loosely into it down to the mucous membrane of the mouth. Healing takes place by secondary intention. The improvement in the general condition of the patient immediately following the opening of the submandibular space, and even before he has left the operating table, is often rapid and striking. The tenseness and anxiousness are gone, the breathing is free, and the entire physical appearance is brighter.

There are those<sup>7, 17, 18</sup> who advocate resection of the submaxillary gland. We have no quarrel with them, but we insist that the main objective is the adequate relief of tension in the confined space. All other considerations and technical procedures are secondary. In our group the submaxillary gland was removed only twice. Indeed, in the whole series the origin of the infection could be directly attributed to the submaxillary gland in only two instances and these, strangely enough, were



not the ones in which the glands were excised. Others<sup>14</sup> recommend that the drainage be instituted through the mucous membrane of the floor of the mouth. Although this approach may be possible in isolated instances, we believe that on the whole it is neither satisfactory nor feasible. Unless free pus is present, adequate exploration through the floor of the mouth may be difficult under any circumstance. This is especially true when trismus and an edematous ligneous tongue make it practically impossible to enter the mouth. In view of the current widespread and often unrestrained use of the sulfonamides, it is not surprising that these drugs have been employed in Ludwig's angina. Several reports<sup>9, 13</sup> have already appeared describing their successful use in this disease, and advocating them as substitutes for surgical intervention. This procedure is dangerous and does not recognize where the true threat of the disease lies. Sulfonamides may and should be used as adjuncts to the treatment, but nothing should replace immediate surgical decompression of the submandibular space.

The urgency of early surgical intervention has been referred to already. The operation should be performed as soon as possible after the diagnosis is made. In this series the decompression was carried out immediately after admission to the hospital in thirty-two cases; on the day after admission in six; on the second day in five; and on the fourth day in three. The delay, where present, was occasioned by uncertainty as to the true nature of the disease and by the fact that some of the patients had spent one or more days on another service in the hospital before they were seen by the consulting surgeon.

The operation was performed under regional novocain infiltration anesthesia in forty-two of the forty-six procedures. The novocain ( $\frac{1}{2}$  per cent) was injected into the skin and subcutaneous tissues along the proposed line of incision. The deeper structures in the neck were found to be remarkably insensitive to pain, and the superficial infiltration was often sufficient in itself to permit the entire procedure to be carried out without discomfort. However, there was no hesitation in injecting additional novocain into the deep cervical fascia and the mylohyoid muscle when necessary. In four instances general inhalation anesthesia was used. Two were in children, five and seven years old respectively, in whom it was difficult to obtain adequate cooperation. The remaining two were in the same adult, a man 63 years of age, who had an associated suppurative cavernous sinus thrombophlebitis, and who was totally irrational and uncooperative. It cannot be too strongly urged that inhalation anesthesia should be avoided as far as possible. The struggling and spasm during the stages of induction, the increase in the secretion of mucus in the pharynx and larynx, and the relaxation of the tense and strained accessory muscles of respiration all conspire to jeopardize the freedom of the respiratory pathway. Intratracheal intubation anesthesia is often impossible due to trismus and a swollen tongue, which

mechanically prevent adequate passage of the tube. Indeed, under any circumstances a preliminary deep anesthesia is often required before intubation is possible. However, even when technically feasible, this method is not without danger, for the tube may aggravate an existing edema of the larynx and lead to its complete closure. Williams and Marcus<sup>24</sup> have recognized and emphasized the dangers of inhalation anesthesia and have substituted intravenous barbiturates (evipal and pentothal) as the ideal anesthetic agents. They concede that these drugs have certain disadvantages,<sup>5, 16, 19, 20, 22, 24</sup> but they believe that the disadvantages can be overcome. A study of their method,<sup>24</sup> however, with all of its complicated and extensive precautions, far from establishes the safety of these intravenous anesthetic agents. Nor does it reveal any particularly significant advantages over inhalation anesthesia. Indeed, in eight of their cases where intravenous anesthesia had been utilized, an emergency tracheotomy had to be performed on the operating table in two instances. They "feel strongly that the proper operative procedure in Ludwig's angina is too extensive to be attempted under local anesthesia."<sup>24</sup> Our experience certainly does not support this view.

There were two deaths in the group. At autopsy one of these patients was found to have a cavernous sinus thrombophlebitis, with pneumonia and lung abscess, in addition to the submandibular infection. The other had a dissecting aortic aneurysm which had ruptured into the thorax. This latter death cannot properly be ascribed to the angina, but inasmuch as it occurred before the patient left the hospital it is included in the mortality figures. There were no instances of mediastinitis. Pneumonia, so often recorded in other series, may in a large measure be traced to the thick mucoid secretions which lie in the pharynx and larynx, and which can be easily aspirated into the lungs in the course of a general anesthesia, inhalation or intravenous. It is our belief that the virtual absence of pneumonia in our group of cases may be directly attributed to the fact that the operations were performed early in the disease and that the procedures were carried out under local anesthesia.

#### CONCLUSIONS

Ludwig's angina is a surgical emergency and demands immediate operation. The cardinal symptoms appear early in the disease and can be easily recognized. They include (1) a tender swelling in the submandibular area of the neck; (2) elevation of the tongue; and (3) edema of the floor of the mouth. The high mortality in this disease is due not to some overpowering and occult virulence of the infecting organisms, but more often to a mechanical obstruction of the respiratory pathway. The primary object of the operation is to relieve and preferably to prevent this obstruction by releasing the tension within the submandibular space. This can be accomplished with safety and certainty only by complete transection of the deep cervical fascia and the

mylohyoid muscle. A thorough decompressive procedure should be performed as soon as possible after the diagnosis is made. Except in extremely extenuating circumstances, the operation should be performed under local novocain anesthesia.

## REFERENCES

1. Ashhurst, A. P. C.: Ludwig's Angina, J. A. M. A. 92: 500, 1929.
2. Ashhurst, A. P. C.: Ludwig's Angina, Arch. Surg. 18: 2047, 1929.
3. Blassingame, C. D.: Angina Ludovici; Anatomic and Clinical Study, Arch. Otolaryng. 8: 159, 1928.
4. Burke, John: Angina Ludovici; Translation, Together With a Biography of Wilhelm Frederick von Ludwig, Bull. Hist. Med. 7: 1115, 1939.
5. Cameron, W. A.: Pentothal Sodium as an Intravenous Anesthetic, Anesth. & Analg. 16: 230, 1937.
6. Collier, F. A., and Yglesias, L.: Infections of the Lip and Face, Surg., Gynec. & Obst. 60: 277, 1935.
7. Colp, R.: Treatment of Deep Infections of Submaxillary Triangle, S. Clin. North America 13: 315, 1933.
8. Davis, G. G.: Acute Septic Infection of the Throat and Neck; Ludwig's Angina, Ann. Surg. 44: 175, 1906.
9. Fulghum, J. E.: Sulfanilamide Treatment of Ludwig's Angina, U. S. Nav. M. Bull. 36: 58, 1938.
10. Grodinsky, M.: Retropharyngeal and Lateral Pharyngeal Abscess, Ann. Surg. 110: 177, 1939.
11. Grodinsky, M.: Ludwig's Angina; Anatomical and Clinical Study With Review of Literature, SURGERY 5: 678, 1939.
12. Grodinsky, M.: Ludwig's Angina; Retropharyngeal Abscess, J. A. M. A. 114: 18, 1940.
13. Hendricks, W. C.: Surgery or Sulfanilamide in Ludwig's Angina, M. Rec. 150: 415, 1939.
14. Houser, K. M.: Ludwig's Angina; Intra-oral Incision in Infections of the Floor of the Mouth, Arch. Otolaryng. 16: 317, 1932.
15. Ludwig, W. F. von: Ueber eine in neuerer Zeit wiederholt hier vorgekommene Form von Halsentzündung, Med. Cor-Bl. d. württemb. ärztl. Landesver. Stuttg. 6: 21, 1836.
16. Lundy, John S.: Intravenous Anesthesia, Am. J. Surg. 34: 559, 1936.
17. Ramsdell, E. G.: Ludwig's Angina. Advantages of Submaxillary Resection, S. Clin. North America 14: 315, 1934.
18. Rehn, E.: Die Behandlung der Ludwigsches Phlegmone durch Exstirpation der Glandula Submaxillaris, Klin. Wchnschr. 1: 2138, 1922.
19. Ruth, H. S., Tovell, R. M., Milligan, A. D., and Charleroy, D. K.: Pentothal Sodium; Is Its Growing Popularity Justified? J. A. M. A. 113: 1864, 1939.
20. Sise, L. F.: Clinical Evaluation of Some Nonvolatile Anesthetic Drugs, New England J. Med. 219: 349, 1938.
21. Thomas, T. T.: Ludwig's Angina, Ann. Surg. 47: 161, 335, 1908.
22. Van Wagenen, W. P., and Costello, C. V.: Sublingual Phlegmon; Primary and Secondary Ludwig's Angina, Ann. Surg. 87: 684, 1928.
23. Williams, A. C.: Ludwig's Angina, Surg., Gynec. & Obst. 70: 140, 1940.
24. Williams, A. C., and Marcus, P. S.: The Choice of Anesthesia in Ludwig's Angina, Anesth. & Analg. 20: 160, 1941.
25. Yerger, C. F.: Ludwig's Angina, Illinois M. J. 49: 168, 1926.

## THE CLINICAL SIGNIFICANCE OF GAS IN THE GALL BLADDER

H. McCORKLE, M.D., AND E. E. FONG, M.D., SAN FRANCISCO, CALIF.

(From the Divisions of Surgery and Roentgenology of the University of California Medical School and the San Francisco Hospital)

THE circumstances under which gas appears spontaneously in the gall bladder are unusual. In rare instances it has been found at operation and at autopsy. In 1901, Stolz reported three autopsies at which gas was found in the gall bladder, and Brutt (1923) and Kirchmayr (1925) recognized cases of gaseous cholecystitis at operation. More recently a few cases have been recorded in which gas in the gall bladder and biliary ducts was visualized by x-ray. This was first reported in 1929, by von Friedrich.

There appear to be two main causes for the spontaneous appearance of gas in the gall bladder. The first of these is infection of the gall bladder with gas-forming bacteria. The second is the passage of gas from the intestine into the gall bladder through a fistula between the gall bladder and the gastrointestinal tract. Gas may enter the bile passages at operation or may be injected into them during cholangiography, but these latter sources are of relatively less diagnostic significance at present than is the spontaneous filling of the gall bladder with gas. In the last two years we have had six cases in which the spontaneous appearance of gas in the gall bladder was demonstrated by x-ray. Three of these cases were caused by anaerobic gas-forming bacteria and three by cholecystenteric fistulae. From reports in the literature and elsewhere we found twenty-one cases, eight of which fall into the first group, and thirteen into the second. The etiology and clinical course of the two types of cases are quite different. Each type requires separate consideration before the significance of gas in the gall bladder can be realized.

1. *Acute Gaseous Cholecystitis*.—This is a rare form of acute cholecystitis associated with infection of the gall bladder with gas-producing bacteria. It also has been designated as "emphysematous cholecystitis," "pyopneumocholecystitis," and "gas phlegmon of the gall bladder." The bacteria most frequently associated with this condition are gas-forming anaerobes of the *Clostridium* group. *Bacillus coli* is also frequently found. Acute gaseous cholecystitis is exemplified by the following cases:

mylohyoid muscle. A thorough decompressive procedure should be performed as soon as possible after the diagnosis is made. Except in extremely extenuating circumstances, the operation should be performed under local novocain anesthesia.

## REFERENCES

1. Ashhurst, A. P. C.: Ludwig's Angina, J. A. M. A. 92: 500, 1929.
2. Ashhurst, A. P. C.: Ludwig's Angina, Arch. Surg. 18: 2047, 1929.
3. Blassingame, C. D.: Angina Ludovici; Anatomie and Clinical Study, Arch. Otolaryng. 8: 159, 1928.
4. Burke, John: Angina Ludovici; Translation, Together With a Biography of Wilhelm Frederick von Ludwig, Bull. Hist. Med. 7: 1115, 1939.
5. Cameron, W. A.: Pentothal Sodium as an Intravenous Anesthetic, Anesth. & Analg. 16: 230, 1937.
6. Coller, F. A., and Yglesias, L.: Infections of the Lip and Face, Surg., Gynec. & Obst. 60: 277, 1935.
7. Colp, R.: Treatment of Deep Infections of Submaxillary Triangle, S. Clin North America 13: 315, 1933.
8. Davis, G. G.: Acute Septic Infection of the Throat and Neck; Ludwig's Angina, Ann. Surg. 44: 175, 1906.
9. Fulghum, J. E.: Sulfanilamide Treatment of Ludwig's Angina, U. S. Nav. M. Bull. 36: 58, 1938.
10. Grodinsky, M.: Retropharyngeal and Lateral Pharyngeal Abscess, Ann. Surg. 110: 177, 1939.
11. Grodinsky, M.: Ludwig's Angina; Anatomical and Clinical Study With Review of Literature, SURGERY 5: 678, 1939.
12. Grodinsky, M.: Ludwig's Angina; Retropharyngeal Abscess, J. A. M. A. 114: 18, 1940.
13. Hendricks, W. C.: Surgery or Sulfanilamide in Ludwig's Angina, M. Rec. 150: 415, 1939.
14. Houser, K. M.: Ludwig's Angina; Intra-oral Incision in Infections of the Floor of the Mouth, Arch. Otolaryng. 16: 317, 1932.
15. Ludwig, W. F. von: Ueber eine in neuerer Zeit wiederholt hier vorgekommene Form von Halsentzündung, Med. Cor-Bl. d. württemb. ärztl. Landesver. Stuttg. 6: 21, 1836.
16. Lundy, John S.: Intravenous Anesthesia, Am. J. Surg. 34: 559, 1936.
17. Ramsdell, E. G.: Ludwig's Angina. Advantages of Submaxillary Resection, S. Clin. North America 14: 315, 1934.
18. Rehn, E.: Die Behandlung der Ludwigsches Phlegmone durch Exstirpation der Glandula Submaxillaris, Klin. Wehnsehr. 1: 2138, 1922.
19. Ruth, H. S., Tovell, R. M., Milligan, A. D., and Charleroy, D. K.: Pentothal Sodium; Is Its Growing Popularity Justified? J. A. M. A. 113: 1864, 1939.
20. Sise, L. F.: Clinical Evaluation of Some Nonvolatile Anesthetic Drugs, New England J. Med. 219: 349, 1938.
21. Thomas, T. T.: Ludwig's Angina, Ann. Surg. 47: 161, 335, 1908.
22. Van Wagenen, W. P., and Costello, C. V.: Sublingual Phlegmon; Primary and Secondary Ludwig's Angina, Ann. Surg. 87: 684, 1928.
23. Williams, A. C.: Ludwig's Angina, Surg., Gynec. & Obst. 70: 140, 1940.
24. Williams, A. C., and Marcus, P. S.: The Choice of Anesthesia in Ludwig's Angina, Anesth. & Analg. 20: 160, 1941.
25. Yerger, C. F.: Ludwig's Angina, Illinois M. J. 49: 168, 1926.

ately surrounding the gall bladder. The gall bladder was enlarged, tense, gangrenous, and jet black in color. There was no visible gross perforation. About 20 c.c. of thin turbid brown green fluid were aspirated from the gall bladder. It contained no calculi. Cholecystostomy was performed. At the time of operation no observations for the presence of gas were made and none was noted.

On the first postoperative day the temperature rose to 104° F. and the pulse rate to 120. The abdomen became distended and the patient appeared very ill. On the following day, some edema and emphysema developed about the wound and extended over the lower thoracic wall. The patient became delirious, fell out of bed, and died a few minutes later.

At autopsy there was no evidence of injury from the fall. Extensive emphysema and edema of the right abdominal and thoracic walls were present, as well as infection of the wound, gangrene of the gall bladder, and general peritonitis.

Bacteriologic study of the contents of the gall bladder showed slender gram-positive and gram-negative rods on direct smear, and *B. coli* and large anaerobic gas-producing bacilli resembling *Cl. welchii*, on culture.

CASE 2—E. B., a white man 59 years of age, gave a history of having had for thirty years recurring attacks of gnawing epigastric pain relieved by food and soda. One month before entry he had an attack of cramping pain in the right upper quadrant of the abdomen, with nausea and vomiting, of one day's duration. A week later he had another attack, more severe than the first, and the pain radiated through to the back. His present attack began one day before entry, with severe cramping pain in the right upper quadrant. The patient vomited once but had no chill. The upper part of the abdomen was moderately tender throughout with some guarding. A tender rounded mass was palpable beneath the right costal margin. The patient appeared to be acutely ill. The temperature was 102 degrees and the pulse rate 96. The white blood count was 13,200, with 96 per cent polymorphonuclear cells. Test of the serum amylase showed 315 units, and the icterus index was 8.7 units a short time after his entry.

The plain x-ray film of the abdomen taken Oct. 29, 1940, about twenty-four hours after the onset of his illness, showed nothing more than evidence of gas in the hepatic flexure of the colon (Fig. 2A). On the evening of the same day isodioidikon was given intravenously as a test of liver function and in an attempt to visualize the gall bladder. The patient apparently had a reaction from the dye, with a chill and high fever which subsided promptly. X-ray examination the following morning showed that the gall bladder had not filled with dye, but was clearly outlined by a shadow of gas surrounded by a well-defined concentric gaseous ring (Fig. 2B). On the following day (Oct. 31, 1940) a film with the patient in the upright position demonstrated a fluid level below the gas (Fig. 2D), apparently in the gall bladder. On Nov. 1, 1940, one therapeutic dose of polyvalent gas gangrene antitoxin was given. A course of sulfathiazole was administered between November 1 and November 7. After four or five days the acute process subsided. The pain, tenderness, and spasm diminished and after the first week of his illness the patient had no complaints. The temperature gradually declined to normal on Nov. 7, 1940, and the patient remained afebrile thereafter. The leucocyte count, which never exceeded 13,400, gradually returned to normal by November 12. The stools were examined for the passage of biliary calculi, but none was found. Duodenal drainage was performed on November 23. Direct smear of the bile obtained from this drainage showed numerous large, long, gram-positive rods and, on culture, *B. coli* and anaerobic spore-forming rods of the *Clostridium* group were found. Frequent x-ray studies of the gall bladder showed the continued presence of gas and fluid therein, gaseous infiltration of its wall, and some extension of the

CASE 1.—D. C., a colored man 49 years of age, became ill on Dec. 27, 1939, with severe, intermittent, generalized, cramping abdominal pain which settled first in the right lower quadrant and then localized in the right upper quadrant and the right flank. He vomited three times. Two years before, the patient had had a similar but milder attack which subsided spontaneously. The general physical examination forty-eight hours after the onset of the illness was not remarkable except for the abdomen and back. There was moderate tenderness in the right upper quadrant with slight rebound tenderness, but the maximum tenderness was present in the right flank. The temperature was 101.8° F. and the pulse rate 90. The white blood count was 21,000, with 90 per cent polymorphonuclear cells. Urinalysis was negative except for a trace of albumin and glucose.



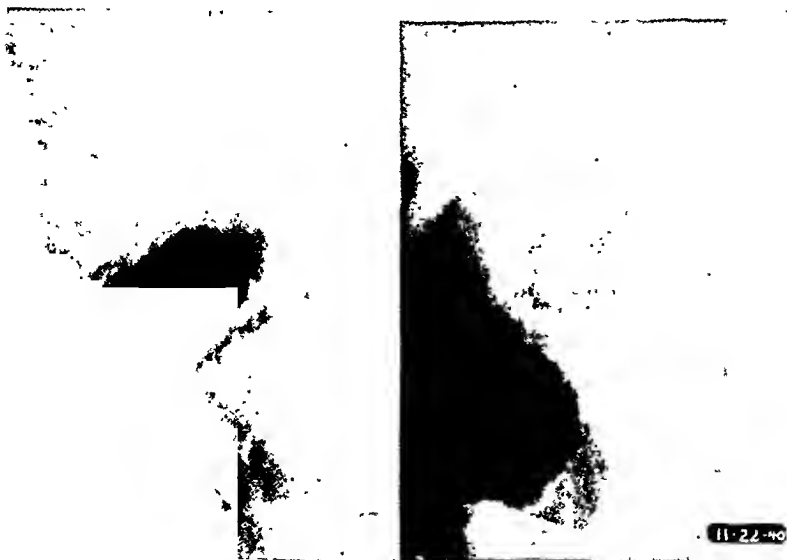
Fig. 1.—Case 1. Gaseous cholecystitis. Plain x-ray film of the abdomen showing gas in the lumen of the gall bladder forty-eight hours after the onset of acute cholecystitis. A gangrenous gall bladder was drained and the patient died about forty-eight hours after operation of a fulminating anaerobic gas bacillus infection of the peritoneum and abdominal wall.

The preoperative diagnosis was acute cholecystitis or acute retrocecal appendicitis. A plain x-ray film of the abdomen showed no evidence of renal or biliary calculi. The pyriform or roughly elliptic shadow of gas which was seen in the right upper quadrant in the x-ray film (Fig. 1) was not recognized at that time as possibly representing a gas-filled gall bladder. It was almost a year later that one of us recalled this case and the x-ray film, in connection with a study of our second case.

Operation was performed Dec. 30, 1939, under ether anesthesia, through a right rectus incision. There was a small amount of turbid fluid in the peritoneal cavity. The omentum was adherent to the under surface of the liver in the region of the gall bladder and there was some green-yellow fibrin in this area. The lower part of the abdomen and operative field were walled off with laparotomy pads. About 25 c.c. of brown-grey pus were aspirated from an abscess in the omentum immedi-

and 2G) until Feb. 15, 1941, when all evidence of gas in this region had disappeared. Periodic physical examinations have shown no abnormalities.

CASE 3.—S. S., a white male 49 years of age, suffered sharp severe pain in the epigastrium at 6 p.m., March 19, 1941. He vomited several times and the pain shifted from the epigastrium to the right subcostal region where it remained as a constant severe ache. The patient had mild diabetes but had had no previous attacks of biliary disease. Marked tenderness, spasm, and rebound tenderness in the right upper abdominal quadrant were present on physical examination and the gall bladder was palpated as a large, rounded, tender mass. The temperature was 101 degrees and the pulse rate 90. There were 17,100 white blood cells, with 91 per cent polymorphonuclears. Urinalysis was negative.



E.

Fig. 2.

F.

E.—Case 2. This film of the gall bladder was taken five days after the onset of the illness. There is evidence of extension of the gas into the surrounding tissues in some places. There is also disintegration of the original delicate layer of gas in the walls of the gall bladder.

F.—Case 2. X-ray film of the gall bladder region taken about three weeks following the subsidence of symptoms and signs of acute cholecystitis. At this time the patient was ambulatory. The film shows a loss of gas outlining the lumen of the gall bladder. The fluid level has disappeared and there is a diminution in the size of the area involved. The gas has been transformed into a cluster of bubbles of various sizes and shapes.

A roentgenogram of the entire abdomen taken on the day of entry showed a moderate amount of gas in the ascending colon and somewhat more in the transverse colon, but none was present in the gall bladder or bile ducts (Fig. 3A). Cholecystography (by the intravenous method) on the following day showed none of the radiopaque material in the gall bladder. Instead there was a large amount of gas and fluid in the enlarged gall bladder (Fig. 3B). The x-ray film taken with the patient in the erect position showed a fluid level superimposed by gas in the lumen of the gall bladder (Fig. 3C). Peripheral to the contents of the lumen was a continuous fine black line representing a layer of gas in the wall of the gall bladder (Figs. 3B and 3C). Twenty-four hours later the gas in the lumen had increased somewhat and extended medially into the soft tissues. The layer of gas



gas into the tissues surrounding it (Fig. 2E). After his dismissal from the hospital the patient returned at weekly intervals for x-ray examinations which revealed a diminution and shrinking in the extent of gas in the gall bladder region (Figs. 2F

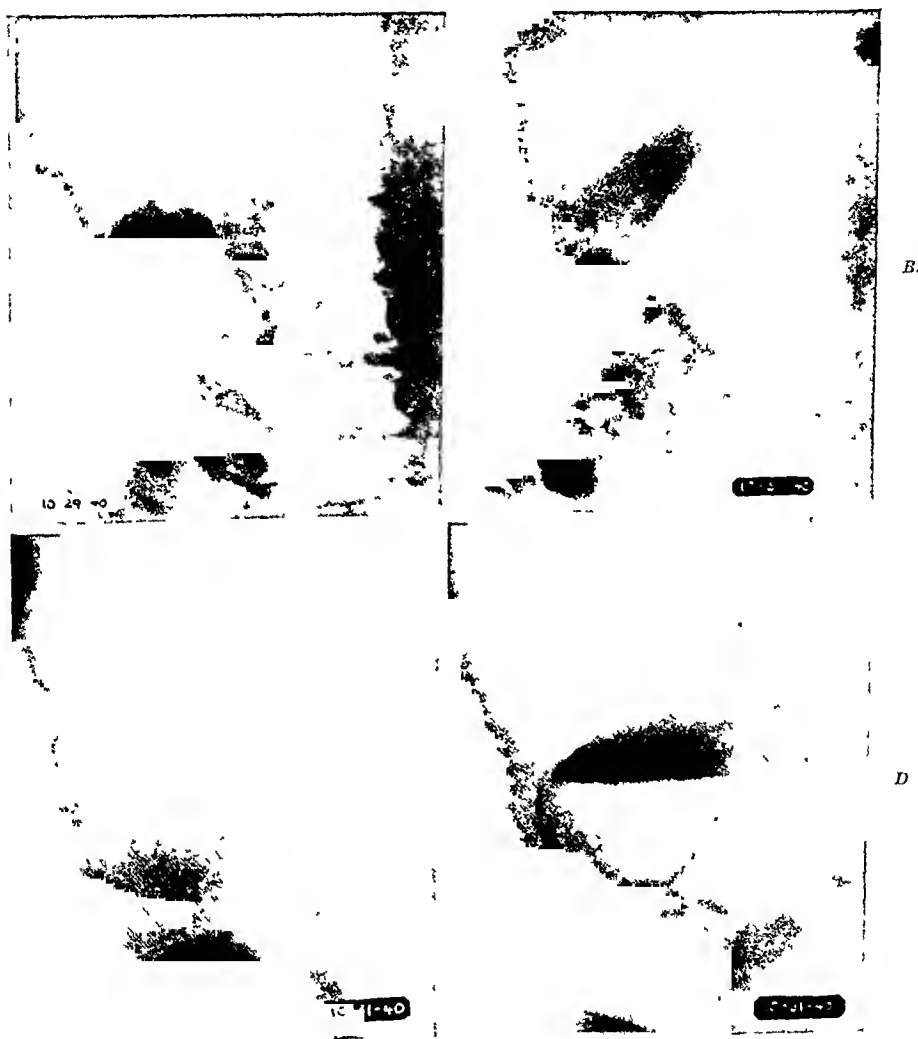


Fig. 2.

A.—Case 2 Plain x-ray film of the abdomen in a case of acute cholecystitis of about twenty-four hours' duration. No gas is seen in the region of the gall bladder, but there is some evidence of gas in the ascending and transverse colon. This is the first of a series of films taken on this patient.

B.—Case 2 Gaseous cholecystitis. Cholecystogram taken thirty-six hours after the onset of acute cholecystitis. The shadow of gas in the upper right abdominal quadrant resembles, in size and shape, a distended gall bladder. The beginning of a concentric gas ring at the periphery of the gall bladder can be seen. This film was made with the patient in the prone position. No radiopaque dye appeared.

C.—Case 2 Film of the gall bladder taken in the prone position seventy-two hours following the onset of acute cholecystitis. The gall bladder is clearly outlined by gas. The concentric ring at the periphery is more definitely seen.

D.—Case 2 Film of the gall bladder taken on the same day as the film shown in Fig. 2C, with the patient upright. This demonstrates gas over fluid in the gall bladder, and gas in the wall as shown by the concentric ring.



in the wall subsequently broke up into numerous short strands and this was accompanied by an increase in the amount of gas outside the gall bladder (Fig. 3D). The process apparently reached its peak about five days after the illness began. Seventeen days after the onset of the acute cholecystitis, the gas in the lumen and wall of the gall bladder had been transformed into many bubbles of various sizes. During the same period the gall bladder was shrinking in size and the pericholecystic gas in the soft tissues was disappearing (Figs. 3A to 3E).

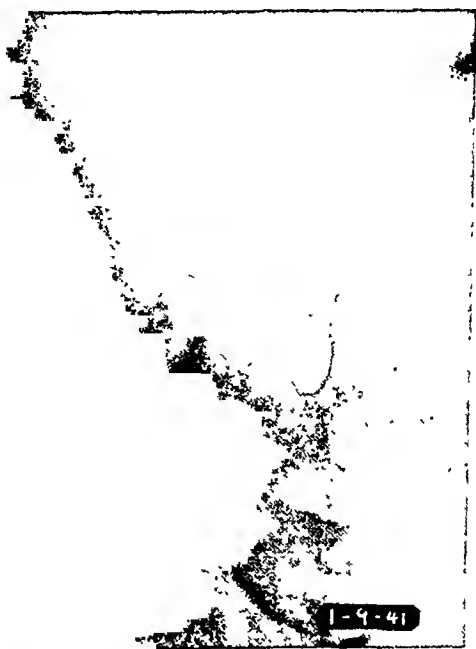


Fig. 2G.—Case 2. Plain x-ray film of the gall bladder region made nine weeks after the subsidence of an attack of acute cholecystitis. At this time the patient was free from symptoms and there were no signs of cholecystitis. The shadows of gas appear in several small groups and the area of involvement is considerably diminished.

The patient was given one therapeutic dose of polyvalent gas gangrene antitoxin and a course of sulfathiazole. Duodenal drainage was performed on March 21, 1941, and, on direct smear, gram-positive rods and cocci in clumps were found; cultures showed anaerobic gas-producing bacilli resembling *Cl. welchii*, *B. coli* and staphylococci. The temperature and leucocyte count subsided to normal over a period of a week and the signs and symptoms of acute cholecystitis resolved rather rapidly during the same time. No calculi were found in the stools. The patient was discharged from the hospital, April 16, 1941. He has had no further symptoms.

Several cases of acute gaseous cholecystitis, similar in many ways to the three just described, have been recorded in the literature.

Simon reported a case of acute gangrenous cholecystitis in a man 32 years old. The roentgenograms in this case showed the distended gas-filled gall bladder with a fluid level and circumferential ring of gas. The diagnosis of acute gaseous cholecystitis was confirmed by cholecystectomy. Sporulating anaerobic bacteria were found in the gangrenous gall bladder.

A case of gaseous cholecystitis in a man 62 years of age was recorded by Hegner. The distended gas-filled gall bladder was visible in the

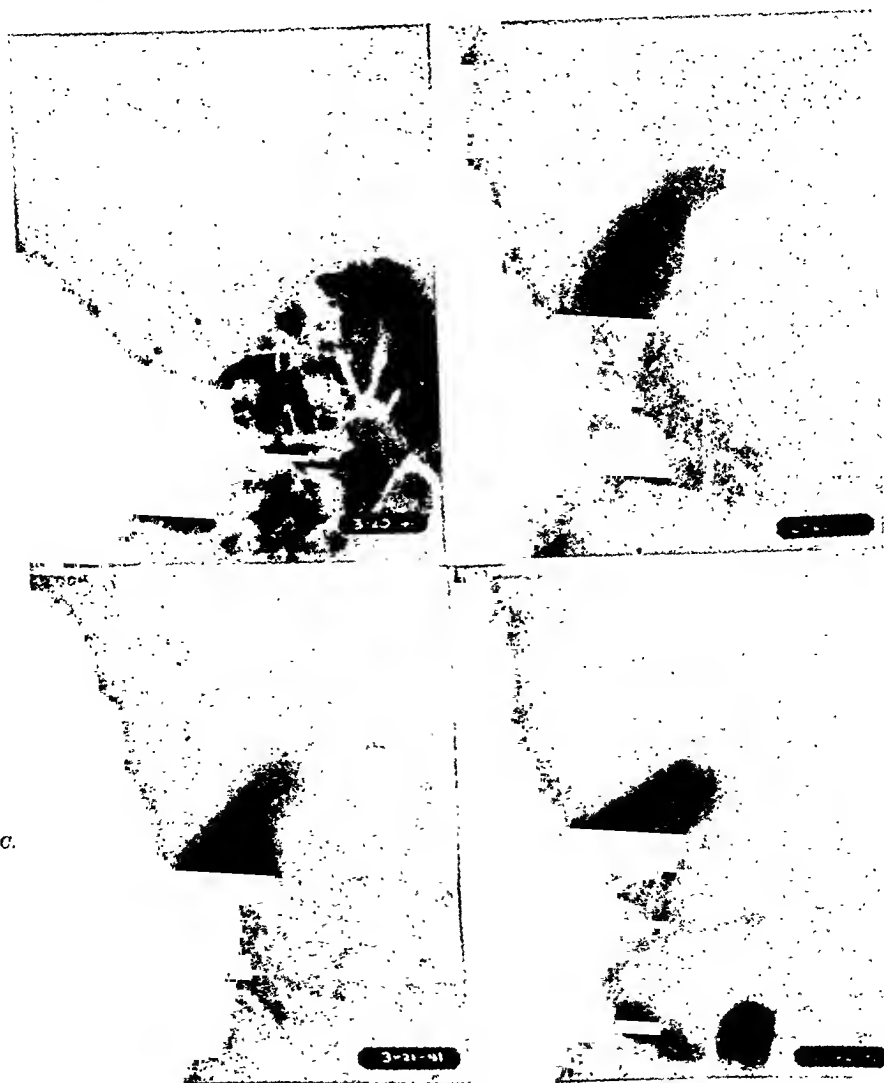


Fig. 3.

A.—Case 3. Plain x-ray film of the gall bladder region in a case of acute cholecystitis of about twenty-four hours' duration. There is no definite evidence of gas in the gall bladder.

B.—Case 3. Gaseous cholecystitis. Cholecystogram (prone position) taken about forty-eight hours following the onset of acute cholecystitis. The gall bladder is seen to be filled with gas and there is a tracing of gas in the wall of the fundus. No radiopaque material is seen. Compare with Fig. 3A.

C.—Case 3. X-ray film of the gall bladder (patient upright) taken on the same day as Fig. 3B. This illustrates a layer of fluid superimposed by gas and a thin line of gas in the wall of the gall bladder two days after the onset of acute cholecystitis.

D.—Case 3. X-ray film of the gall bladder (patient upright) taken on the fourth day following the onset of acute cholecystitis. The gas in the lumen and the fluid level in the fundus of the gall bladder are still seen. There is some evidence of extension of the gas from the wall of the gall bladder into the surrounding tissues.

plain x-ray film of the abdomen. At operation a gas-filled abscess was evacuated. Cultures of pus grew Welch's bacillus. In this case the diagnosis of acute gangrenous cholecystitis was further confirmed by autopsy.

Schmidt reported the case of a patient 37 years old, who had acute cholecystitis. The x-ray films showed the gall bladder filled with gas. Twelve days later it filled faintly with radiopaque material. This case was not confirmed by operation or autopsy. The patient recovered with medical treatment.

Wybauw described a case of acute gaseous cholecystitis in a woman 53 years old, in whom a distended gas-filled gall bladder was demonstrated by x-ray. At operation the wall of the gall bladder contained bubbles of gas.



Fig. 3E.—Case 3. Roentgenogram of the gall bladder about one month following the clinical subsidence of acute cholecystitis. The gas has collected into a small group or cluster of bubbles. The patient was ambulatory and free from symptoms at this time.

Berg reported two cases of acute gaseous cholecystitis but did not illustrate them.

Recently Stevenson and Baird demonstrated the x-ray films of a patient with emphysematous cholecystitis. The diagnosis was made by x-ray examination and the condition was treated by roentgentherapy. These observers also mentioned a second case, in which the treatment was surgical.

It is well known that the *B. coli* and Welch's bacillus may be cultured from the gall bladder in some cases of acute cholecystitis. It is equally

well known that these bacilli, especially the Welch bacillus, may produce gas. Other organisms may produce gas but rarely do so. Magner and Hutcheson collected statistical studies on the bacteriology of cholecystitis and noted the incidence of *B. welchii* as varying from 1 to 22 per cent in cultures from the wall of the gall bladder, and from 0.5 to 6 per cent in cultures of bile from the gall bladder. The same authors quoted the incidence of *B. coli* as varying from 4.5 to 49 per cent in cultures of the wall of the gall bladder, and from 6 to 50 per cent in cultures of the gall bladder bile from patients with cholecystitis. According to Andrews and Henry, *B. coli* is the gas-forming organism most frequently found in the gall bladder (from 11 to 16 per cent); next in frequency is *B. perfringens* (from 9 to 11 per cent of cases). Gordon-Taylor and Whitby determined that *B. welchii* was found in nearly 9 per cent of a series of gall bladders removed at operation. In this group were two cases of acute gangrenous cholecystitis in which the organism (*B. welchii*) was found in pure culture.

In the cases of acute gaseous cholecystitis discussed in this report it appears that the condition is associated with infection of the gall bladder by anaerobic gas-forming bacteria. These bacteria were found in all cases in which it was possible to obtain cultures directly at operation. The similarities of the x-ray and clinical pictures in patients who were not operated upon, together with the somewhat circumstantial evidence obtained from bacteriologic study of the duodenal drainage, appear to justify their inclusion in this group of cases.

In connection with acute gaseous cholecystitis, all of the ways in which infection may spread to and localize in the gall bladder have been considered, namely, hematogenous bacterial embolism, lymphogenous spread, direct extension from contiguous organs (for example, the gastrointestinal tract), and the influx of organisms into the gall bladder bile, either ascending from the duodenum or descending from the liver bile. At present, however, it appears impossible to determine definitely the source of the infection of the gall bladder in these cases of anaerobic gaseous cholecystitis. Speculation is invited, also, upon the difficult question as to why some gas-forming anaerobes are extremely pathogenic in certain instances, milder in others, and apparently inactive under some circumstances. The virulence of the strain of organisms and the resistance of the host are always factors which must be considered. Also, in certain diseased gall bladders there may exist a localized fertile field for the activity of gas-forming organisms; stasis, obstruction, ulceration by calculi, necrosis and anoxia caused by edema, and interference with or occlusion of the vascular supply to the gall bladder are examples. Thus, under certain circumstances of ulceration, obstruction, or interference with the vascular supply, a gall bladder which contains potentially pathogenic forms of these gas-forming anaerobic organisms may become a medium for their successful growth. That such circumstances occur rarely is fortunate.

The onset of acute gaseous cholecystitis has the clinical appearance of a severe form of acute cholecystitis. In the first few hours of a gas-producing infection of the gall bladder there is no roentgenologic evidence of its existence. It usually requires from twenty-four to forty-eight hours before sufficient gas has been produced so that it may be visualized roentgenologically. It is seen first on the x-ray film as a black area forming the outline of the enlarged distended gall bladder. Subsequently, the roentgenologic picture seems to change according to the progression or regression of the inflammatory process in the gall bladder. If the infection subsides the gas is gradually absorbed or possibly discharged through the cystic duct. This is illustrated by Schmidt's case in which the gas was said to have disappeared from the gall bladder within twelve days, the disease subsiding promptly under medical treatment. If, on the other hand, the infection continues, gaseous infiltration of the wall of the gall bladder results. Such infiltration appears as a thin dark layer of gas immediately peripheral to that in the lumen of the gall bladder. As the infectious process progresses, this thin layer of gas becomes broader and disintegrates into numerous short dark strata. At the same time, the amount of gas in the lumen of the gall bladder usually increases in volume. There is likely to be some fluid in the gall bladder in this condition and an x-ray film made with the patient in the erect position often shows a well-defined fluid level. Later in the course of the infection, the gaseous infiltration of the wall of the gall bladder extends into the surrounding tissues and the gas is seen as rounded dark areas. At this stage there is probably pericholecystitis and there may be pericholecystic abscesses containing gas. In the cases of acute gaseous cholecystitis in which the patients recovered, the findings described above were followed by x-ray evidence of a very gradual absorption of the gas. That in the lumen of the gall bladder lost its contour first; there followed shrinkage and disruption of the layers of gas in the wall and lumen of the gall bladder into bubbles of various sizes. These were seen in the x-ray films as clusters of more or less circular dark areas. Evidence of gas in the tissues could be demonstrated by x-ray long after clinical evidence of acute cholecystitis had disappeared. Gas was not seen in the bile ducts in the roentgen-ray films of any patient with gaseous cholecystitis. The two patients treated conservatively have remained well.

The management of cases of acute inflammatory disease of the gall bladder accompanied by x-ray evidence of gas in the gall bladder deserves special consideration. Because of the rarity of the spontaneous occurrence of gas in the gall bladder, no surgeon has had enough experience with this interesting finding to be able to draw any final conclusions about it.

It is difficult to outline a general policy for the management of acute cholecystitis. As a rule, we treat acute cholecystitis conservatively and

prefer to carry out surgical procedures at some elected time after the acute process has subsided. Special consideration, however, is given to the individual problem presented by each patient with cholecystitis and, actually, we often find it necessary to operate early for acute cholecystitis. Each case of acute gaseous cholecystitis merits particularly careful clinical management. The risk of disrupting and disseminating a more or less localized gas bacillus infection by operative manipulations must be weighed against the possibility of perforation of the gall bladder into the free peritoneal cavity. Our unfortunate experience in our first case of this type made us feel that, in future cases, a conservative or expectant course should be pursued even more persistently than usual. The patient described in Case 1 died of a fulminating gas bacillus infection of the abdominal and thoracic walls and peritoneum following cholecystostomy for acute gangrenous gaseous cholecystitis of about 60 hours' duration. He was operated upon because we could not eliminate the possibility of a high retrocecal appendicitis and because we did not recognize at the time that the shadow of gas in the x-ray film represented a distended gall bladder filled with gas. Our second and third cases of acute gaseous cholecystitis were managed with even greater than usual conservatism because of the unfortunate experience with this first patient. We also believe, both because of our experience and the reports of other observers who have seen rare cases in which there was dissemination of gas bacillus infection following operations on the biliary tract, that the usual interval cholecystectomy should not be performed in cases of gaseous cholecystitis. Every effort will be made to avoid operation on the biliary system in the event of later recurrence of symptoms. Though it is scarcely permissible to express an opinion based on such a small experience with acute gaseous cholecystitis, we are inclined to believe that conservative management with supportive treatment should preferably be employed during the acute phase of this disease, and that both early and interval operation should be avoided if possible. It should be mentioned, however, that other observers have reported successful operations in cases of acute gaseous cholecystitis. X-ray therapy has been used in at least one case. The treatment of acute gaseous cholecystitis with polyvalent anaerobic antitoxin, chemotherapy, or x-ray therapy may be indicated, but the efficacy of such measures will probably be as difficult to evaluate in these cases as in other anaerobic gas bacillus infections.

2. *Cholecystenteric Fistulae*.—These are occasionally associated with the spontaneous appearance of gas in the gall bladder. The condition usually demands investigation because of one or more episodes of acute cholecystitis or cholangitis. The x-ray films taken in these cases have shown evidence of gas in the gall bladder and bile ducts in a few instances. This gas probably comes from the intestinal lumen. The following case reports exemplify cholecystenteric fistula with gas in the  
ducts:



CASE 4.—M. S., a woman 35 years of age, had had indigestion and discomfort in the right upper abdominal region all of her life. At operation four years previously, the gall bladder had appeared to be normal, but there was a large cyst of the common duct that was not definitely identified as such at the time. The cyst was drained and an external biliary fistula resulted. Three months after the first operation laparotomy was performed again. A large lycopodium granuloma was removed and an anastomosis between the common duct and the duodenum was performed. The patient remained free from symptoms until about four months before her present entry, when she began to have transient attacks of nausea and pain in the right upper quadrant of the abdomen. She had many such attacks and suffered a chill with one of them. On physical examination no abnormal findings were noted. There was a healed scar in the right upper quadrant. The laboratory findings were within normal limits and the patient was afebrile.



Fig. 4.—Case 4. Choledochenteric fistula. Roentgenogram of a patient who had had a choledochoduodenostomy four years previously. In the last four months she had had attacks of pain in the right upper abdominal quadrant accompanied by nausea and chills. The gas-filled gall bladder can be seen.

Cholecystography was done by the intravenous method. The gall bladder was not demonstrated by the opaque material but in all the films appeared a shadow of gas the size and shape of the gall bladder (Fig. 4). A barium meal showed some reflux of barium into the common duct. Operation was not advised.

CASE 5.—F. P., a woman 54 years of age, had had a cholecystostomy two years previously for recurring episodes of cholecystitis with colic, of twenty-four years' duration. She was then well until eight months before entry, when she began to have attacks of severe pain in the right upper abdominal quadrant with chills, nausea and vomiting, fever to 105° F. at times, and jaundice. She lost fifty pounds in weight in eight months. At the time of entry she was not jaundiced. She was obese and there was moderate tenderness beneath the right costal margin. The laboratory findings were not remarkable.

The gall bladder did not fill with the opaque solution given for cholecystography, but a collection of gas was seen in the gall bladder (Fig. 5A). A barium meal showed 95 per cent gastric residue after three hours. A small amount of barium was seen in the gall bladder (Fig. 5B) and the duodenal bulb did not fill. At operation a very hard mass, about 6 cm. in diameter, was found in the region of the pylorus and gall bladder. It was bound down by firm scar tissue to the stomach, liver, duodenum, and transverse colon. In an attempt to free this mass, a fistula between the gall bladder and stomach was encountered. The gall bladder contained numerous small faceted calculi. A biopsy of the tissue was taken and a report of adenocarcinoma was made. Because of the poor condition of the patient the opening in the stomach was sutured, an anterior gastroenterostomy was done and the gall bladder was drained. The patient died of peritonitis; autopsy was not granted.

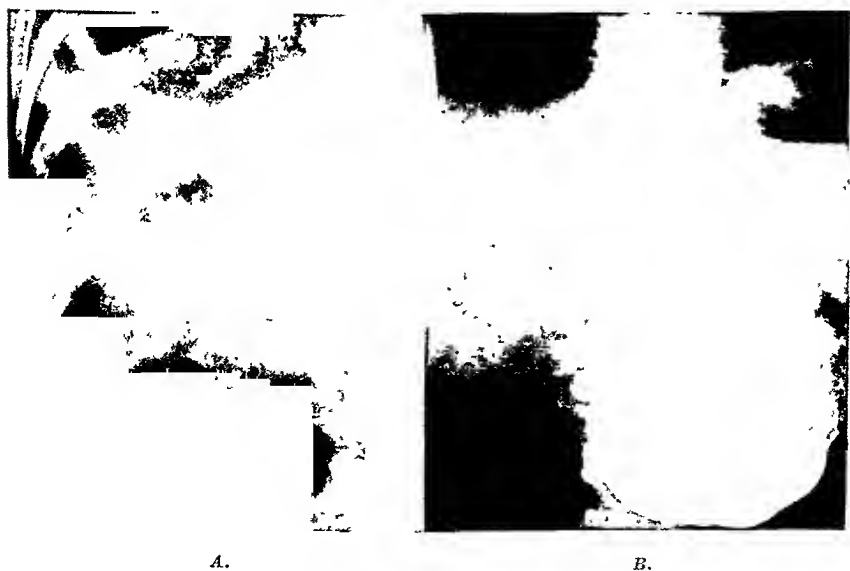


Fig. 5.

A.—Case 5. Cholecystogastric fistula. X-ray film showing gas in the gall bladder of a patient who had a cholecystogastric fistula demonstrated at operation. The cause of the fistula was malignant ulceration of the stomach involving the gall bladder.

B.—Case 5. Following a barium meal, the gall bladder shown in Fig. 5A is partly filled with barium and gas.

CASE 6.—A. S., a woman 41 years of age, complained of painless jaundice of twelve days' duration. At operation, May 31, 1940, carcinoma of the head of the pancreas was found. A palliative cholecystoduodenostomy was done.

One and one half years later the patient returned to the University Hospital. At that time she complained of recurrent episodes of nausea and severe pain in the right upper quadrant of the abdomen. The pain radiated to the back and was accompanied by a sensation of epigastric distention. This attack was of two weeks' duration. There was tenderness throughout the abdomen, most acute in the right upper quadrant. While the patient was in the hospital she had repeated attacks of severe pain in the right upper quadrant, with vomiting. Her temperature rose to 102.2° F. on several occasions.

X-ray examination showed the gall bladder, common duct, and hepatic ducts to be filled with gas. A barium meal showed marked contrast between the intestine

and the gas-filled bile ducts but none of the opaque material entered the bile ducts. The patient died two months later. At autopsy carcinoma of the ampulla of Vater with extension into the pancreas was found.

Several cases of cholecystenteric fistula with x-ray evidence of spontaneous filling of the gall bladder or bile ducts with gas, similar to the three cases just described, are reported in the literature.



Fig. 6.—Case 6  
gall bladder and  
carcinoma of the

ampulla of Vater fistula. Roentgenogram showing gas in the  
gall bladder and bile ducts of a patient  
who had had a cholecystoduodenostomy for  
half years previously.

Von Friedrich described two cases in which the gall bladder, common duct, and hepatic ducts were filled spontaneously with gas. One of the patients had previously had a surgical cholecystoduodenostomy for carcinoma of the pancreas. The second patient had a spontaneous cholecystoduodenal fistula associated with cholelithiasis. In both cases attention was directed to the condition because of episodes of acute cholangitis, and the presence of gas in the gall bladder and ducts was discovered by x-ray examination. Henry described a case of choledochoduodenal fistula with gas in the common, hepatic, and cystic ducts. Pohlandt reported a case of cholecystogastric fistula secondary to cholelithiasis in which gas was found in the gall bladder, common duct, and hepatic ducts. Powers described three cases of cholecystoduodenal fistula caused by cholelithiasis, in which gas was demonstrated in the biliary ducts. Berg reported six cases of fistula between the bile ducts and intestine, in which gas was found in the biliary tract. Three of them were caused by chole-

lithiasis, two were associated with duodenal ulcer, and one was caused by carcinoma of the stomach.

The simplest and most obvious way that gas may enter the bile ducts from the intestinal tract is through a surgical anastomosis between them. Spontaneous fistulae between the gall bladder and various parts of the intestinal tract, notably the duodenum, stomach, and colon, are known to occur and they also are potential sources of gas in the gall bladder and bile ducts. The possibility of regurgitation of gas from the duodenum into the biliary ducts and gall bladder by way of the ampulla must also be considered in connection with this phenomenon. With our present information, it is impossible to say whether or not it has occurred. Berg attempted the retrograde filling of the bile ducts with air and gas, but without success. The rare instances in which barium has been reported to have passed from the duodenum into the bile passages at examination by barium meal, and the isolated cases in which foreign bodies have undoubtedly entered the gall bladder from the intestinal tract through apparently normal bile passages, make the possibility of this source of gas in the bile passages a matter for consideration.

It is probable that the gas appearing in the bile ducts and gall bladder comes from the gases that normally exist in the intestinal lumen, and that it enters through the stoma of the cholecystenteric communication. The possibility must be considered, however, that anaerobic gas-forming bacteria, introduced into the gall bladder and bile passages through a fistulous opening in the gastrointestinal tract, might grow in the bile passages and produce gas in a manner similar to that described above for the first type of case (gaseous cholecystitis). No record was found of a proved case of this type.

Under circumstances other than surgical anastomosis between some part of the bile passages and the gastrointestinal tract, the presence of gas in the gall bladder or bile ducts may be strongly suggestive of spontaneous fistula between these tracts. In such cases the patient's course often suggests chronic disease in the gall bladder with episodes of severe cholecystitis, cholangitis, colic, or intestinal obstruction. Since these patients usually have had disease of the gall bladder for some time, it is not surprising that the gall bladder tends to be either normal in size or somewhat smaller than usual, and that the bile ducts appear somewhat larger than would be expected normally. The commonest cause of these fistulae is probably calculous cholecystitis with infection and ulceration of the gall bladder. Rarely, peptic or neoplastic ulceration may produce cholecystenteric fistula. Further confirmation of the presence of such a fistula may sometimes be accomplished by the use of barium enema or barium meal. The discovery in the stool of very large calculi of biliary origin is also valuable confirmatory evidence of cholecystenteric fistula.

When the gall bladder or bile ducts are filled with gas they may be visualized by x-ray examination and this serves as a valuable means of

establishing the diagnosis of cholecystenteric fistula. In these cases the bile duets as well as the gall bladder are usually, though not always, outlined in gas.

The treatment of patients with cholecystenteric fistula in which there is evidence of communication between the bile passages and some portion of the gastrointestinal tract, as manifested by gas in the gall bladder or bile duets, is essentially the same as that outlined elsewhere for such fistulae. Expectant or conservative treatment during the acute phase would, therefore, be in order, unless intestinal obturation by a biliary calculus causing intestinal obstruction occurred. Many of these fistulae have been reported to have healed spontaneously. If operation must eventually be done in a case of cholecystenteric fistula, a quiescent period will probably offer a more favorable opportunity to correct the lesion and effect repair.

3. *Differential Diagnosis.*—The differential diagnosis of cases in which gas is found in the gall bladder on x-ray examination is usually not difficult. The clinical picture of the onset of acute disease of the biliary tract in the two types of cases in which gas appears spontaneously in the gall bladder may be somewhat similar at the onset of the condition. The x-ray findings and the subsequent clinical and roentgenologic courses of the two types of conditions, however, are usually different. In a case of cholecystenteric fistula with gas in the gall bladder, the gall bladder is likely to be normal in size, or small, and the bile duets as well as the gall bladder contain gas visible on x-ray examination. In cases of infection of the gall bladder with anaerobic gas-forming organisms the x-ray film usually shows an enlarged or distended gas-filled gall bladder without evidence of gas in the duets. In the anaerobic type a fluid level may be seen in films taken in the upright position. In addition, a ring of gas outlining the gall bladder is usually observed. Neither of these has been found in cases of fistula. The changes suggesting disintegration of the gas in the gall bladder, its spread into surrounding tissue, and later absorption are characteristic of anaerobic gas-producing infections of the gall bladder and are not found in cases of cholecystenteric fistula. The use of barium contrast medium may help to confirm the presence of fistula.

The x-ray appearance of the circumferential ring of gas present in acute gaseous cholecystitis may be simulated by lipomatosis of the wall of the gall bladder. Kommerell reported such a case. The reason for the similarity is that lipomatous tissue, possessing a density less than that of surrounding viscera, may also appear black against a light background on the x-ray film, just as gas does. This, however, can be differentiated from gaseous infiltration by the changes which occur from day to day in the cases of gas infection, while lipomatosis of the wall of the gall bladder maintains a uniform appearance. Furthermore, there will be no gas or fluid level in the gall bladder in the case of lipomatosis.

## SUMMARY

There are two types of pathologic conditions in which the spontaneous appearance of gas in the gall bladder may be demonstrated roentgenologically. The first occurs as a result of an acute infection of the gall bladder with anaerobic gas-forming bacteria. The second is the result of an abnormal communication between the gall bladder or bile ducts and some part of the gastrointestinal tract. Air may enter the gall bladder or bile ducts during surgical procedures on those structures or during cholangiography, but at the present time this source is considered to be of little diagnostic significance.

In every case reviewed in this report an episode of acute cholecystitis led to the discovery of gas in the gall bladder. X-ray examination is essential for the diagnosis. The x-ray and clinical findings in both types of cases are described and illustrated.

Conservatism is the keynote in the therapeutic management of the cases in which gas in the gall bladder results from anaerobic gas-producing infection. It also seems desirable to pursue an expectant course in cases in which a cholecystenteric fistula is suggested by a gas-filled gall bladder, allowing opportunity for the acute inflammatory process to subside and a chance for the fistula to close spontaneously before operation is undertaken.

## REFERENCES

1. Andrews, E., and Henry, L. G.: Bacteriology of Normal and Diseased Gall-bladders, *Arch. Int. Med.* 56: 1171, 1935.
2. Berg, H. H. (Hamburg, Germany) quoted by Rigler, L.: Report of the Fifth International Congress of Radiology in Chicago, Ill., *Surgery* 3: 159, 1938.
3. Berg, H. H.: Gasfüllung der Gallenwege, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 61: 1-9, 1940.
4. Brutt, H.: Gasbacilleninfektion des Pankreas und Pankreasnekrose, *Virchow's Arch. f. path. Anat.* 246: 33-41, 1923.
5. Eliason, E. L., and Stevens, L. W.: Spontaneous Internal Biliary Fistula, *Am. J. Surg.* 51: 387-392, 1941.
6. Gordon-Taylor, G., and Whithy, L. E. H.: A Bacteriological Study of Fifty Cases of Cholecystectomy With Special Reference to Anaerobic Infections, *Brit. J. Surg.* 18: 78-82, 1930-31; The Incidence of Anaerobic Infections in the Gallbladder 19: 619-621, 1931-32.
7. Hegner, C. F.: Gaseous Pericholecystitis With Cholecystitis and Cholelithiasis, *Arch. Surg.* 22: 993, 1931.
8. Henry, Lucas: Hepatic and Cystic Duets Visualized by Spontaneous Filling With Gas and Barium, *Radiog. & Clin. Photog.* 9: 9-10, 1933.
9. Judd, E. S., and Burden, V. G.: Internal Biliary Fistula, *Ann. Surg.* 81: 305-312, 1925.
10. Kirchmayr, L.: Ueber einen Fall von Gasbrand der Gallenblase, *Zentralbl. f. Chir.* 52: 1522, 1925.
11. Kommerell, B.: Lipomatose der Gallenblase im Röntgenbild, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 61: 308-309, 1940.
12. Magner, W., and Hutcheson, J. M.: Cholecystitis. A Bacteriological and Experimental Study, *Canad. M. A. J.* 27: 469-477, 1932.
13. Pohlandt, Klaus: Gallenblasen-Magenfistel nach Steindurchbruch, *Bruns' Beitr. z. klin. Chir.* 159: 138-147, 1934.
14. Powers, R. A.: Air in the Hepatic Duets; an X-ray Sign of Biliary Fistula, *Radiology* 27: 474-478, 1936.

15. Schmidt, E. A.: Emphysematous Cholecystitis and Pericholecystitis, *Radiology* 31: 423-427, 1938.
16. Simon, Joseph: Le Pyopneumocholécyste et son Diagnostic Radiologique, *Presse méd.* 40: 1938-1940, 1932.
17. Stolz, A.: Ueber Gasbildung in den Gallenwegen, *Virehow's Arch. f. path. Anat.* 246: 33-41, 1923.
18. von Friedrich, L.: Luft in den Gallenwegen als diagnostisches Merkmal, *Fortsehr. a. d. Geb. d. Röntgenstrahlen* 39: 616-619, 1929.
19. Wakefield, E. G., Vickers, P. M., and Walters, W.: Cholecysto-enteric Fistulae, *SURGERY* 5: 674-677, 1939.
20. Walters, W., and Snell, A. M.: Diseases of the Gallbladder and Bile Ducts, Philadelphia and London, 1940, W. B. Saunders Co., pp. 61, 127-128, 162-164.
21. Wybauw, L.: Image Vesiculaire Inhabituelle, *J. Belge Gastro-enterol.* 4: 123-125, 1936.

## THE SURGICAL TREATMENT OF CARCINOMA OF THE STOMACH IN AGED INDIVIDUALS

RALPH F. BOWERS, M.D., NEW YORK, N. Y.

(From the New York Hospital and Cornell University Medical College)

**D**URING the past decade there has been a growing interest in the surgical attack upon carcinoma of the stomach. The use of x-ray therapy alone, which at first seemed to offer sufficient palliation to justify its application at least in those cases which were considered inoperable, has proved to be disappointing and it has become obvious that the only hope in obtaining five-year or permanent cures, or definite palliative relief lies in gastric resection.

The more or less hopeless attitude toward radical gastric resection which was present in the 1900's was largely based upon a high mortality rate and a belief that actual help to the patient did not justify the use of this dangerous procedure. But with the passage of time, cases are now known to have survived ten, twelve, fifteen, twenty and twenty-two years following the radical operation. Actually, the number of cases reported is small but the fact remains that these people lived because of the operation and that alone. It is true that some of these long-lived cases died eventually of metastases distant in location from the gastrointestinal tract. Thus, some hopelessness still persists today, but the present results do not support such profound pessimism. Cooper,\* in a recent article, states that 44 per cent of operable cases have survived five years. The cases which died before the expiration of five years in large proportion were improved and their symptoms greatly relieved for from one to four years. When one realizes that the patients who were explored but not subjected to resection had to endure nine months of starvation, debility, and weakness before death, the chance for cure or five-year cure, or even several years of comfortable living should not be disregarded. It must be pointed out that those patients who survive resection even though cure is not to be expected, die within four years postoperatively, but their lives prior to death are often normal and their death, due to metastases to the lung or liver or generalized carcinomatosis, is frequently not attended with prolonged starvation.

Physicians who are familiar with the natural course of the disease know that carcinoma in the aged individual exhibits a slower growth

Presented at the meeting of the Society of University Surgeons, Cincinnati, Ohio, Feb. 12-14, 1942.

\*Cooper, W. A.: Problem of Gastric Cancer, J. A. M. A. 116: 2125-2129, 1941.



15. Schmidt, E. A.: Emphysematous Cholecystitis and Pericholecystitis, *Radiology* 31: 423-427, 1938.
16. Simon, Joseph: Le Pyopneumocholécyste et son Diagnostic Radiologique, *Presse méd.* 40: 1938-1940, 1932.
17. Stolz, A.: Ueber Gasbildung in den Gallenwegen, *Virehow's Arch. f. path. Anat.* 246: 33-41, 1923.
18. von Friedrich, L.: Luft in den Gallenwegen als diagnostisches Merkmal, *Fortsehr. a. d. Geb. d. Röntgenstrahlen* 39: 616-619, 1929.
19. Wakefield, E. G., Vickers, P. M., and Walters, W.: Cholecysto-enteric Fistulae, *SURGERY* 5: 674-677, 1939.
20. Walters, W., and Snell, A. M.: *Diseases of the Gallbladder and Bile Ducts*, Philadelphia and London, 1940, W. B. Saunders Co., pp. 61, 127-128, 162-164.
21. Wybauw, L.: Image Vesiculaire Inhabituelle, *J. Belge Gastro-enterol.* 4: 123-125, 1936.

## THE SURGICAL TREATMENT OF CARCINOMA OF THE STOMACH IN AGED INDIVIDUALS

RALPH F. BOWERS, M.D., NEW YORK, N. Y.

(From the New York Hospital and Cornell University Medical College)

**D**URING the past decade there has been a growing interest in the surgical attack upon carcinoma of the stomach. The use of x-ray therapy alone, which at first seemed to offer sufficient palliation to justify its application at least in those cases which were considered inoperable, has proved to be disappointing and it has become obvious that the only hope in obtaining five-year or permanent cures, or definite palliative relief lies in gastric resection.

The more or less hopeless attitude toward radical gastric resection which was present in the 1900's was largely based upon a high mortality rate and a belief that actual help to the patient did not justify the use of this dangerous procedure. But with the passage of time, cases are now known to have survived ten, twelve, fifteen, twenty and twenty-two years following the radical operation. Actually, the number of cases reported is small but the fact remains that these people lived because of the operation and that alone. It is true that some of these long-lived cases died eventually of metastases distant in location from the gastrointestinal tract. Thus, some hopelessness still persists today, but the present results do not support such profound pessimism. Cooper,\* in a recent article, states that 44 per cent of operable cases have survived five years. The cases which died before the expiration of five years in large proportion were improved and their symptoms greatly relieved for from one to four years. When one realizes that the patients who were explored but not subjected to resection had to endure nine months of starvation, debility, and weakness before death, the chance for cure or five-year cure, or even several years of comfortable living should not be disregarded. It must be pointed out that those patients who survive resection even though cure is not to be expected, die within four years postoperatively, but their lives prior to death are often normal and their death, due to metastases to the lung or liver or generalized carcinomatosis, is frequently not attended with prolonged starvation.

Physicians who are familiar with the natural course of the disease know that carcinoma in the aged individual exhibits a slower growth

Presented at the meeting of the Society of University Surgeons, Cincinnati, Ohio, Feb. 12-14, 1942.

\*Cooper, W. A.: Problem of Gastric Cancer, J. A. M. A. 116: 2125-2129, 1941.

of the original tumor, a less rapid advance of the metastatic lesions and, therefore, a longer course before the disease advances sufficiently to cause the death of the individual. Therefore, it would seem that aged individuals have a better chance for permanent cure or at least more prolonged palliation than younger people. It is because of this that we have renewed our interest in attacking these serious lesions in the aged, as well as in the young or middle age group.

TABLE I

STATISTICS ON GASTRIC CANCER IN PERSONS OVER 60 YEARS OF AGE (1932-1940)

	NUMBER OF CASES	OPERATIVE DEATHS
No operation	49 (47.0%)	
Explored, but not resected	23 (22.0%)	2 ( 8.7%)
Explored and resected	11 (10.6%)	1 ( 9.0%)
Palliative gastric resection	6 ( 5.9%)	3 (50.0%)
Palliative gastroenterostomy	11 (10.6%)	5 (45.5%)
Miscellaneous operations:	4 ( 3.9%)	2 (50.0%)
2 gastrostomies (1 operative death)		
1 total gastrectomy (1 operative death)		
1 gastroenterostomy (no operative deaths)		
Total	104	13 (23.6%)

TABLE II

STATISTICS ON ALL GASTRIC CANCER CASES (1932-1940)

Total number of cases			289
Patients not operated upon			99
Operations: (Two patients had 2 operations)			192
	NO.	OPERATIVE DEATHS	
Explored	98	8 ( 8.2%)	
Gastric resection	42	5 (11.9%)	
Palliative gastric resection	20	3 (15.0%)	
Palliative gastroenterostomy	23	6 (26.0%)	
Miscellaneous	9	6 (66.7%)	
Patients dead			(82.4%) 238

In Tables I and II are collected the data on 289 cases of gastric cancer, 104 of which involved patients over 60 years of age. Attention is called to the fact that the mortality in the resected cases of persons over 60 years is 9 per cent as against 11.9 per cent for the entire group. The mortality is higher in the aged group on whom palliative gastric resection is performed. Also, palliative gastroenterostomy is not only attended by a high mortality rate but is notably unsuccessful in relieving the patient.

The present low mortality rate deserves attention. In the 1920's the mortality rate in gastric resection for carcinoma ranged from 25 to 40 per cent. A study of the chief causes of death responsible for this high mortality rate shows that they were pneumonia, evisceration, pneumonia plus evisceration, general debility, and circulatory accidents. The in-

telligent use of sulfapyridine combats pneumonia to the point where it is now much less dangerous a complication, and although all cases cannot be saved by its use, the number of deaths due to postoperative pneumonia is decreasing. Also, in combatting pneumonia there is less coughing, less dyspnea, less abdominal distention, and consequently less strain on the sutured wound, and therefore this probably reflects itself locally by decreasing the number of cases of evisceration. Through-and-through silver wire in approximating the wound also is a safeguard against evisceration for it tends to maintain the integrity of the wound in the presence of infection. Postoperative embolism is still an important factor, and as the other complications decrease in severity it is more apparent as a cause of death than it was previously. In this age group we have kept the patients in bed immediately following operation, but now we often allow them out of bed and walking in three or four days following operation. Whether this prevents embolus formation is not proved, yet the fact that not one of these patients died of embolus or had clinical pulmonary emboli suggests that this treatment may have added something to their prevention. Also, with the increasing use of heparin it is to be hoped that this very serious complication may be limited still further.

It is to be noted that in the pre- and postoperative phase measures are carried out which seem to be very helpful in preventing serious trouble. In patients with carcinoma one is impressed with the fact that there is a low acidity and that there is a heavy bacterial growth on the ulcerated lesion. Consequently, wound infection and peritonitis are much more commonly seen in patients with carcinoma as compared with those with ulcer, in whom the same operation is often used. More attention should be given to the fact that the carcinomatous stomach is an infected stomach. Wangensteen had developed a closed technique for gastric resection because of the high incidence of infection. The measures that may be used to help prevent serious infections are lavage decompression when obstruction is present, and the administration of sulfaguanidine or sulfadiazine previous to the operation. The results of this therapy will probably show a small incidence of infection. Full vitamin balance can now be obtained in a very short time and should be utilized in these cases preoperatively. Fluid balance in the dehydrated patient and high caloric intake by supplementary glucose, clyses and infusions are also important. A study of the circulatory system of these aged individuals and a correction by the use of digitalis and other drugs if necessary is a valuable preoperative aid. It is important in the preoperative phase that the patient be ambulatory in order to prevent stasis of the circulation.

*Diagnostic Aids.*—It is obvious that early operation in aged individuals is as essential as in other groups if good results are to be obtained. The history of the patient is often the most important and

effective lead to an early diagnosis. The insidiousness of the disease and the apparent neglect of the individual to become interested in his symptoms are well known. The physician also may not be impressed because the symptoms of loss of appetite, anorexia and weakness, may be considered the result of age rather than the manifestations of an organic lesion. The physical examination in the early stage may fail to reveal anything of note and the physician may be deceived because the physical examination seems negative. Any patient with a history of loss of appetite, aversion to food, loss of weight, and weakness must be suspected of having gastrointestinal carcinoma until proved otherwise if we are to diagnose the early cases. Laboratory aids are helpful but not in themselves positive. Gastric analysis in about 90 per cent of the patients shows a low gastric acidity, but there are 10 per cent in whom the acid may be high. Bacteriologic studies of the gastric juice are helpful. Patients with ulcer very seldom show a high titer of bacteria, but in carcinoma the Boas-Oppler bacillus as well as numerous pyogenic organisms can be found in the gastric juice. The finding of blood in the gastric juice may or may not be helpful. Stool examination reveals occult blood in a high percentage of the cases, but this is not always present. X-ray examination is extremely helpful, but one must not depend on the x-ray examination alone because in a very small early lesion, particularly on the greater curvature but also in the prepyloric region and upon the lesser curvature, it may be overlooked in the early stages. The x-ray examination also may be misleading in that it may appear to show a hopeless cancer of the stomach which at operation is demonstrated to be an early resectable lesion. Therefore, x-ray must not be relied upon completely as to the presence or operability of gastric carcinoma. Gastroscopic examination which has been so enthusiastically advocated by Schindler and has been adopted in most of the clinics in the country also is a valuable adjunct, but again has its limitations. The prepyloric region of the stomach can quite accurately be examined, but there are parts of the lesser curvature which cannot be seen even though the growth at that site may be large. Gastroscopists, as a result of their examinations, have stated that a lesion was hopelessly inoperable when at operation we have been able to do a successful radical resection.

In reviewing the diagnosis of early carcinoma as determined by our experience, it is apparent that neither a careful history or physical examination nor any of the laboratory aids are individually conclusive but, taken together, serve to establish the diagnosis of cancer in a fairly high proportion of cases. In a small proportion of cases, exploratory laparotomy appears still to be a justifiable procedure.

*Anesthesia.*—The choice of anesthesia in this group of cases is difficult to make and varies in the hands of different operators because no one rule can be applied to all cases. Local anesthesia can be used in

some, but it must be borne in mind that certain of these elderly individuals will show a definite reaction to the use of novocain, and we have had to abandon the operation because of such reactions in two patients. Gas-ether anesthesia raises the blood pressure and may be a contributory factor in some of the vascular accidents, therefore it has not been generally used. Open-drop ether has been found to be satisfactory even in those cases with cardiac involvement. We have felt that avertin is too depressing in these individuals, and that spinal anesthesia with its resultant lowering of the blood pressure in a great number of cases may be a factor contributing to vascular disturbances in patients of this age group. Consequently, local anesthesia, if it is possible to use it, or open-drop ether are in our experience the anesthetics of choice.

*Procedure.*—The operative procedure used is the usual radical resection either of the Billroth type II when the tumor is small and in the pyloric region or of the Polya-Hofmeister type, making the anastomosis either retro- or antecolic depending upon the anatomic relations that exist. The Hofmeister operation has been a very successful one in our hands. We have not used the closed type of operation in any of our cases.

*Postoperative Care.*—For a period of twenty-four to forty-eight hours nothing is given by mouth and the fluid balance is maintained by clyses and infusions. One ounce of water by mouth per hour is begun between twenty-four and forty-eight hours postoperatively and this is gradually increased until the patient is taking a six-feeding soft diet at the end of one week. In some cases we have increased this much more rapidly without ill effect. With through-and-through wires present in the wound, one is able to allow the patient out of bed as soon as the postoperative reaction has subsided. It is important to continue vitamin intake as well as to maintain the fluid balance. The sulfonamide therapy usually is continued four to five days postoperatively, provided there are no signs of toxicity, and then it is abandoned. The silver-wire stitches are removed from the fifteenth to twentieth day, and the patient is discharged from the hospital on any balanced diet that he desires. It seems obvious that the measures that are now utilized in the pre- and postoperative phases are contributing to a low mortality rate.

#### DISCUSSION OF CASES

CASE 1.—Dr. H., aged 68 years. A nine-month history of anorexia, loss of weight, loss of energy, and general malaise had been recognized by this physician as symptoms of carcinoma of the stomach. He was opposed to operation and did not consult a physician until at the end of nine months the symptoms, plus vomiting, became so marked that he begged for any relief that could be offered. The physical examination and all objective tests indicated that the lesion was hopelessly inoperable with peritoneal carcinomatosis. Exploratory laparotomy was performed and the

stomach was found to be completely involved. There were metastases in the liver, omentum, regional glands, and peritoneum. Because of the distressing vomiting, a site on the anterior aspect of the stomach was chosen for gastroenterostomy, which did not function satisfactorily, and the patient succumbed on the twelfth day of bronchopneumonia. The case demonstrates a physician who thought it was hopeless to ever have gastric resection performed for carcinoma of the stomach and chose to die rather than have the operation, but became so miserable that he begged for operation at a time when all chance of recovery or palliation was gone.

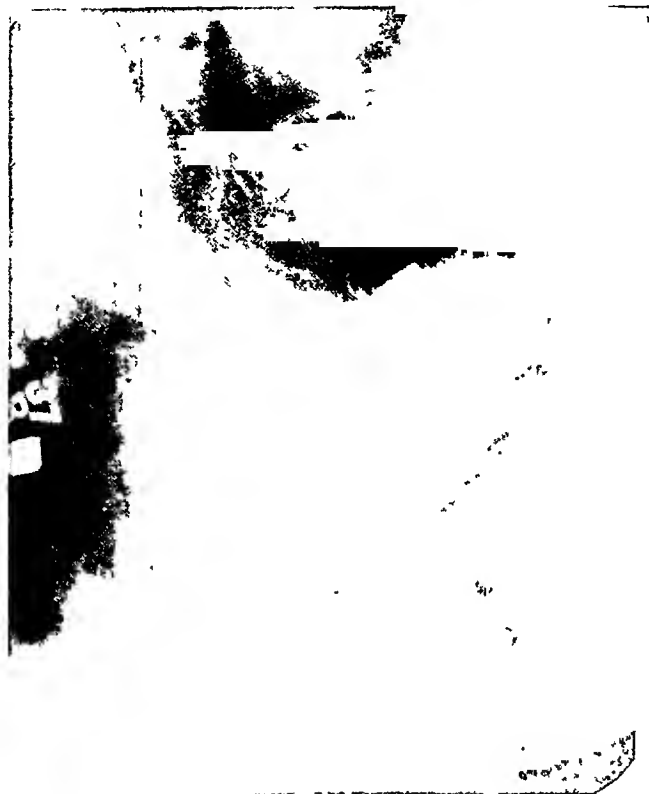


FIG. 1.—Case 1. Dr. H.

CASE 2.—Mr. S., aged 60 years. This was a patient with severe cardiac disease, who had been treated at the Rockefeller Institute for a period of over two years for intermittent cardiac decompensation. For ten months previous to admission he had developed, along with his cardiac symptoms, anorexia, weight loss, and weakness. Carcinoma of the stomach was suspected but his physicians did not consider operation because of his severe cardiac disease. At the end of ten months of these symptoms, however, the cardiac phase had improved and it appeared that he was dying now from starvation. X-ray showed a large lesion in the prepyloric region which was considered to be so advanced that operation was thought to be a mere gesture. Under local anesthesia supplemented by open-drop ether, exploration was performed. The lymph nodes along the lesser curvature, as well as several places in the liver, contained small metastases. Gastric resection was done and his postoperative course

was uneventful. He lived without gastric symptoms for two years and four months following the operation. One cannot say that he did not die of carcinoma, but his palliation was real.

CASE 3.—Mrs. D., aged 65 years. This woman had had a cholecystectomy for gallstones with biliary colic three years previous to the onset of the gastric symptoms. While performing the cholecystectomy the operator explored the abdomen and found nothing pathologic in the stomach or other organs, with the exception of the gall bladder. Two years later this patient began to complain of indigestion of the type which she herself felt was different from the indigestion that attended the gall bladder disease and she immediately sought the advice of her physician about it. Her family physician, knowing that her original trouble was gallstones, thought she might be having indigestion associated with biliary tract disease, corrected her



Fig. 2.—Case 2., Mr. S.

diet, and waited for one month. At the end of this time the symptoms persisted in spite of the dietary correction, so he made laboratory studies which showed a low gastric acidity, occult blood in the stools, and a small but definite neoplastic involvement of the prepyloric area in the x-ray. After the proper preparation, exploration was done under ether anesthesia. The lesion was movable and there were a few small involved glands on the lesser curvature. A Hofmeister resection was easily performed. There was a mild wound infection but no fear of evisceration because of the presence of silver wires. Now, twelve months following the operation she is in good health, but having some difficulty with eating large amounts comfortably.





Fig. 4.—Case 5., Mrs. B.



Fig. 3.—Case 3., Mrs. D.

CASE 4.—Mrs. McD., aged 70 years. This is a woman who had been perfectly healthy all her life and had never had to consult a physician, who began to have anorexia, loss of weight, and weakness fifteen months before admission. One month before admission, while vacationing in Vermont, she had a large gastric hemorrhage, evidenced by the vomiting of large amounts of blood, as well as passing tarry stools. She recovered from the hemorrhage, and on examination showed loss of weight, anemia, a large mass in the left upper quadrant, and also inability to take at that time a teaspoonful of water without regurgitation. The gastric juice showed

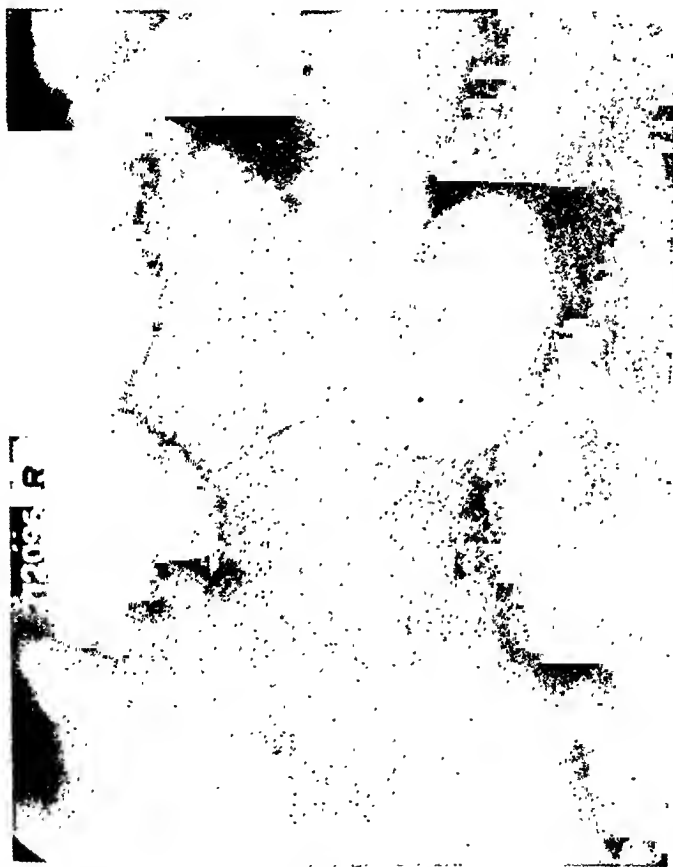


Fig. 5.—Case 6., Mrs. S.

fresh blood and no acid. The stools were positive for blood and the x-ray showed a huge lesion involving almost the entire stomach. On exploration under ether anesthesia there was a huge carcinoma involving all of the stomach except about two inches in the cardiac region. The lymph nodes along the lesser curvature were extensively involved. One or two metastatic areas in the liver were found. Because of her inability to take even water, a gastric resection was done, but it was necessary to leave some of the involved glands. She developed bronchopneumonia on the forty-eighth hour, was given sulfapyridine, and promptly recovered. A mild infection of the wound developed but this cleared upon drainage. This patient lived six

months following the operation, and up to two weeks before her death was able to eat all kinds of soft foods with comfort.

CASE 5.—Mrs. B., aged 58 years. This patient had suffered from dyspepsia for ten years. Three years before admission her indigestion became more marked, she lost her appetite, lost weight, and was unable to eat even small amounts of food without feeling "full." She did nothing about this until she had lost twenty pounds in weight and became so weak that she could not do her housework. Physical examination showed only loss of weight and tenderness in the epigastrium. There was no free acid, but there was persistent occult blood in the stools. X-ray examination showed a fairly large neoplasm in the prepyloric area, which was explored, and was easily movable and resected radically. Her postoperative course was uneventful and she is now living, five years following the operation. She still has what seems to be the initial indigestion, but has maintained her weight and vigor.



Fig. 6.—Case 7., Mr. H.

CASE 6.—Mrs. S., aged 78 years. Accurate history was difficult to obtain due to language difficulties, but for seven months the patient had had marked weight loss, weakness, lack of appetite, and debility. Physical examination showed emaciation and a tumor mass in the left epigastric region which moved on respiration. Gastric

analysis revealed no acid and stools were positive for occult blood. X-ray showed a large neoplastic involvement of the midportion of the stomach with obstruction. Considerable hesitancy was felt about operating on this patient on account of her age and emaciation. However, exploratory laparotomy was done under ether anesthesia and a radical gastric resection performed with ease. No metastases were found. She had an uneventful convalescence and is living and well fourteen months after operation.



Fig. 7.—Case 8., Mr. C.

CASE 7.—Mr. H., aged 65 years. This patient had a ten months' history of "going downhill." He had mild epigastric pain, a poor appetite, and marked weakness. Examination showed an anemic, emaciated man with a palpable mass in the epigastrium. Gastric analysis revealed no free acid and stools were positive for blood. X-ray showed a large tumor in the prepyloric region and gastroscopy confirmed this. Exploratory laparotomy was done under ether anesthesia and a Hofmeister procedure carried out. The patient had an uneventful recovery with the exception of phlebitis which cleared quickly without special treatment. He is living and well ten months after operation.

CASE 8.—Mr. C., aged 73 years. For one year this patient had been complaining of epigastric pain, and discomfort after eating. He lacked appetite and had lost

weight. Several days before admission to the hospital he began to have fever, chills, and persistent vomiting. Examination revealed a very sick man with a temperature of 39° C. and a picture of an acute condition of the abdomen with rigidity and tenderness in the upper quadrant of the abdomen. With conservative measures the patient recovered from this episode but still continued to run a fever, occasionally vomited, and lost more weight. Gastric analysis revealed no acid and the stools were positive for occult blood. X-ray examination showed extensive neoplastic involvement of almost the entire stomach and gastroscopic report stated that the lesion was hopelessly inoperable. Exploration was done under ether anesthesia, the entire tumor was easily delivered, and a high almost total gastric resection was accomplished. There were no complications and the patient is alive and well, one year and two months following the operation.



FIG. 8.—Case 9, Mrs. MacD.

CASE 9.—Mrs. MacD., aged 82 years. This patient had had indigestion for the past two and one-half years, the underlying suspected condition being gallstones. She was treated by dietary measures for this, but finally she herself began to notice a movable "ball" in the upper abdomen. All this was attended with lack of appetite, loss of weight, and vomiting on occasions. Stool examination was negative for occult blood and the gastric analysis was omitted. The x ray picture showed a large circumscribed rarified lesion in the region of the pylorus. After a short period of preparation with vitamin therapy and correction of her dehydration, exploration was done under ether anesthesia combined with local infiltration. The en-

tire stomach was easily delivered and a Hofmeister radical gastric resection was performed. The patient was up and out of bed on the third day and ate regular food on the fifth day. Her recovery was entirely uneventful and she is now living and well, nine months after operation.

#### SUMMARY

From a study of these cases evidence is accumulated which strongly suggests that far from hopeless results may be anticipated in the aged patient with carcinoma of the stomach, and that with prompt recognition of the condition and proper preparation, operation can be safely done with results, if anything, better than in the younger age groups.

## TRANSTHORACIC ESOPHAGOGASTROSTOMY

CRANSTON W. HOLMAN, M.D., AND BARTON MCSWAIN, M.D.,  
NEW YORK, N. Y.

(From the Department of Surgery of the New York Hospital and Cornell University Medical College)

THE primary object of this report is to comment upon the technical features of an esophagogastrostomy performed upon a patient with carcinoma of the stomach and lower end of the esophagus. The unexpected, successful immediate result demonstrates that this procedure may be used to good advantage for the treatment of esophageal carcinoma that involves any part of the esophagus distal to the bifurcation of the trachea. Transthoracic esophagogastrostomy is now an accepted method of treatment for lesions of the lower third of the esophagus and, although Ochsner and DeBakey,<sup>1</sup> in 1941, collected only seven successful cases, the number now is considerably higher. The operation to be described demonstrates the usefulness of this procedure, also, for lesions of the middle third of the esophagus. Other papers (Carter and Stevenson,<sup>2</sup> Garlock,<sup>3</sup> and Adams and Phemister<sup>4</sup>) may be consulted for a complete review of the treatment of carcinoma of the esophagus.

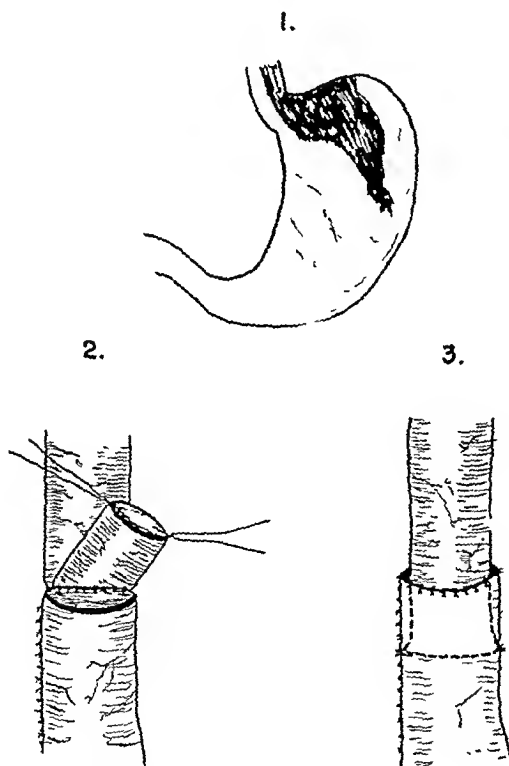
CASE REPORT.—A white male, 66 years of age, entered the New York Hospital with symptoms of weakness, loss of weight, lower substernal pain of eight months' duration, and vomiting of one week's duration. Physical examination showed a chronically ill man but otherwise was not remarkable. A lesion of the cardiac end of the stomach was demonstrated by x-ray.

Abdominal exploration on June 23 revealed a carcinoma of the posterior wall of the cardiac end of the stomach that extended from the esophageal opening distally for a distance of approximately four inches (see Fig. 1). After satisfactory exposure of the lesion was obtained by mobilizing the upper end of the stomach and dividing the left gastric artery, it was decided that a transthoracic approach would greatly facilitate the removal of the lesion.

Abdominal distention delayed the transthoracic procedure until July 9, sixteen days later. At this time the chest was opened through an intercostal incision in the seventh intercostal space and the seventh to fifth ribs inclusive were divided posteriorly. The lower end of the esophagus was mobilized, following which the diaphragm was opened. It was found that the stomach, spleen, and liver were closely adherent to each other and to the diaphragm, so that it was difficult to establish a line of cleavage. During dissection the splenic vein was injured, which necessitated a splenectomy, but this in turn facilitated the mobilization of the stomach. After division of the vessels along the lesser and greater curvature, the posterior wall of the stomach was removed down to the antrum. From the anterior wall of the stomach a tube, approximately seven inches long, was made and, surprisingly enough, the blood supply appeared to be adequate since the color of the

tube remained good. The esophagus was telescoped into the stomach as shown in Fig. 2. The tube of the stomach reached to the aortic arch without difficulty and, consequently, the anastomosis could be carried out without tension. Stay sutures were inserted, anchoring the esophagus to the stomach tube (see Fig. 3) so that the invaginated end of the esophagus would not roll back, as it has been shown to do in dogs.<sup>2</sup> The sutures at the anastomosis approximated the mucosa of the stomach to the muscularis of the esophagus. Finally, omentum was drawn up and sutured snugly about the anastomosis.

The postoperative course was complicated by a localized empyema which responded well to drainage. The patient was discharged six weeks after operation in relatively satisfactory condition and at this time was eating a regular diet. He died about five months after operation from liver metastases. His personal physician reported that until the time of his death he was able to swallow all foods satisfactorily.



The findings and results in this patient bring up several interesting features. The first concerns the importance of performing the trans-thoracic procedure not more than seven days after the preliminary exploration. In this patient great difficulty was encountered in mobilizing the stomach because of the firm adhesions that had formed within the sixteen days between operations.

On the other hand, in a second patient whose second operation was performed within five days of the preliminary exploration, no technical difficulties were encountered.



CASE REPORT. A 6-year-old woman complained of dysphagia, loss of weight, and subacute pain of one month's duration. General examination was not remarkable. X-rays revealed a lesion at the cardiac end of the stomach involving the lower third of the esophagus. Preliminary exploratory laparotomy was performed June 9, 1941, and transthoracic esophagogastronomy by the method described by Garlock with removal of the lower third of the esophagus and cardiac end of the stomach, June 11, 1941. Mobilization of the stomach was accomplished without difficulty. The patient recovered without complication and is well nine months postoperatively.

The question may arise as to whether or not preliminary laparotomy is necessary. Garlock has pointed out the importance of resting this decision upon the results of preoperative biopsy of the lesion. If the lesion is proved to be adenocarcinoma it can be presumed to have arisen either from the stomach or from gastric mucosa situated at the lower end of the esophagus, and these tumors frequently develop early metastases to the liver. However, if the lesion is of the squamous-cell type it probably arises in the esophagus and such tumors metastasize late and involve the liver infrequently. With this in mind, he concludes that whereas for a squamous-cell lesion laparotomy is not indicated, for adenocarcinoma it definitely is. Certainly if x-ray demonstrates that the lesion involves the stomach, a preliminary laparotomy should be done.

The second point of interest is the satisfactory manner in which healing of the anastomosis took place. As detailed, mucosa of the stomach was sutured to muscularis of the esophagus, since it was impossible to invert the stomach so as to approximate serosa to muscularis. At the time this was thought to be most unsatisfactory and, as an additional precaution, the omentum was drawn up into the chest and securely sutured about the line of anastomosis. This, in addition to the telescoping of the esophagus for 2 cm. into the stomach tube, was considered an important feature in the satisfactory healing that took place. In order to confirm this opinion a limited number of experiments were carried out on dogs.

In one group of eight dogs, esophagogastronomy was performed using a Murphy button to anastomose stomach and esophagus. No omentum was used to reinforce the anastomosis and no sutures were introduced; in this group five of the eight dogs developed a leak at the site of the anastomosis. In a second group of seven dogs, esophagogastronomy was similarly performed using a Murphy button but, in addition, the omentum was used to envelop the line of sutures. No additional sutures were used. In this group only one of the seven animals developed a leak at the anastomosis.

A third point demonstrated by this patient was the apparent failure of a stricture to form, as evidenced by his ability to swallow solid foods without difficulty. As had been shown by the work of Carter and Stevenson, in animals stricture formation is the usual occurrence follow-

ing an anastomosis in which the esophagus is telescoped for a short distance within the stomach. With this in mind, stay sutures were so placed as to anchor the lower end of the esophagus to the wall of the stomach tube, and it may be that these prevented a stricture (Fig. 3).

Finally, we should like to emphasize the practicability of using trans-thoracic esophagogastrostomy for all lesions of the esophagus situated distal to the bifurcation of the trachea. Although in this particular patient a tube was made, in many it is possible to bring the entire stomach high into the chest without difficulty and, if the esophagus is sutured without tension, healing has proved, both clinically and experimentally, to take place readily. At any rate, it would seem that this operation may be performed with anticipation of satisfactory results in approximately 50 per cent of the lesions of the esophagus. Whereas in the past a Torek procedure has been considered the method of choice for lesions of the middle third of the esophagus, it would seem that esophagogastrostomy may be used to greater advantage in some cases, not only from the viewpoint of lower mortality but from the viewpoint of the patient's comfort and satisfaction.

#### REFERENCES

1. Ochsner, A., and DeBakey, M.: *J. Thoracic Surg.* 10: 401, 1941.
2. Carter, B. N., and Stevenson, J.: *J. Thoracic Surg.* 10: 446, 1941.
3. Garlock, John H.: *Surg., Gynec. & Obst.* 70: 556, 1940.
4. Adams, W. E., and Phemister, D.: *J. Thoracic Surg.* 7: 621, 1937-1938.

## THE TREATMENT OF IMPENETRABLE ESOPHAGEAL STRICTURES BY A COMBINED INTRAESOPHAGEAL AND EXTRAESOPHAGEAL APPROACH

E. C. DRASH, M.D., AND FLETCHER D. WOODWARD, M.D.,  
CHARLOTTESVILLE, VA.

*(From the Departments of Surgery and Otolaryngology of the University of Virginia School of Medicine)*

ESOPHAGEAL obstruction is a rather frequent occurrence. Most of the obstructions are due either to cicatricial stenosis resulting from the ingestion (accidental or suicidal) of strong alkalis or acids, carcinoma of the esophagus, diverticula, or cardiospasm. Less frequently, ulcerations occur from other causes such as peptic ulcer, foreign body, or other inflammatory lesions and result in scarring and stenosis of the esophagus. Carcinoma will not be considered in this discussion.

Complete fusion of the esophageal walls resulting from extensive burns is quite uncommon, but multiple areas of stricture are more frequently seen (Case 3). While there may be complete blocking of the esophagus at one point, usually the remainder escapes such severe injury and can be readily dilated by the usual means. The patient with a complete benign esophageal obstruction presents a difficult therapeutic problem for which many procedures have been advocated and tried, including not only diverse methods of attempting to open and enlarge strictures, but also various attempts to construct an artificial esophagus either intrathoracic or extrathoracic.

Most of the latter have resulted in such poor substitutes indeed for the normally functioning esophagus that it seems advisable to restore the esophagus to its normal function whenever this can be accomplished. This contribution presents a new method of accomplishing this end in the cases not amenable to simple methods.

In the University of Virginia Hospital our records show that a total of fifty-two strictures were encountered in forty-six patients. The site of the strictures varied markedly in relation to the accidental or suicidal ingestion of caustics. In the accidental group approximately 52 per cent were in the upper third, 24 per cent were in the middle third, and 24 per cent were in the lower third. In the attempted suicide group, only 14 per cent were in the upper third, 72 per cent in the middle third and 14 per cent in the lower third (Table I and Fig. 1). Obviously

the individuals in this suicidal group were not deterred by taste or odor but swallowed the material with determination. Most of the cases of accidental swallowing of strong caustics occurred in children who tend to expectorate promptly anything with an unsatisfactory taste. In the accident group probably a smaller quantity of material was swallowed and the burn did not extend so far down the esophagus.

TABLE I. THE ETIOLOGY AND LOCATION OF THE 52 STRICTURES, ENCOUNTERED IN 46 PATIENTS

CICATRICAL STENOSIS	UPPER THIRD	MIDDLE THIRD	LOWER THIRD
Lye—accidental	18	8	8
Lye—suicidal	2	10	1
Foreign body—accidental		1	
Ammonia—accidental	1		
Ammonia—suicidal			1
Lime—accidental			1
Acid—accidental	1		
Total—52 cases	22	19	11

Only two patients in our group presented an impenetrable stricture. One of these was in a twelve-year-old colored boy, which followed the accidental ingestion of lye. The other was in an adult who swallowed a large quantity of lye with suicidal intent. This method was also applied in a third case for reasons to be detailed later.

*Early Treatment.*—If these patients are seen immediately after the ingestion of the caustic, treatment can usually prevent the development of an impermeable stricture. The treatment consists of prompt lavage of the faec, mouth, esophagus, and stomach with large quantities of the proper neutralizing solution. A nasal catheter can then be inserted down to the stomach and left in place ten to fourteen days or longer. This may entirely obviate the necessity for a gastrostomy. After three to four weeks the esophagus can be studied by x-ray and any abnormal narrowing noted. If there is any tendency to early stricture, gentle stretching can be done under direct vision through the esophagoscope.

*Late Treatment.*—Inasmuch as most of the cases do not present themselves for treatment until two to four months after the burn of the esophagus, the problem of stricture continues to present itself. Late cases are forced to seek treatment because of pain and increasing difficulty in swallowing, and usually present marked weight loss. Such patients almost invariably need a gastrostomy, both for feeding purposes and for retrograde bouginage. The gastrostomy should be of such a type, and so placed, that bouginage can be readily accomplished. Gastrostomy of a modified Stamm type in the midportion of the stomach performed in two stages is usually satisfactory. The patient is given a string to swallow and the bougies can then be threaded on the lower end of the string after it is brought out through the gastrostomy opening.

The passage of the string may not be an easy task and may require great skill and ingenuity on the part of the physician.\* Many other-

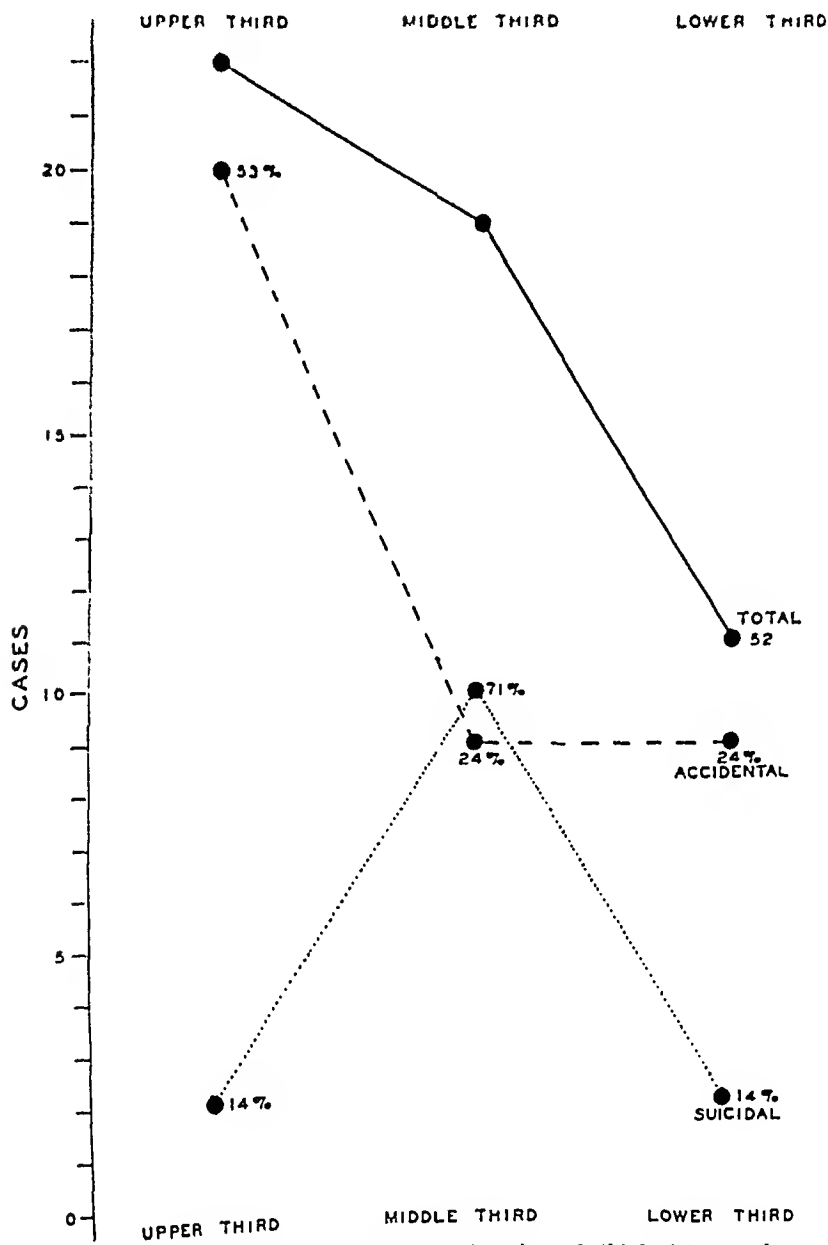


Fig. 1.—A graph showing the location and percentage in each third of the esophagus of the fifty-two strictures.

\*The string end bougie dilatations are conducted in the University of Virginia Hospital and outpatient department by the Department of Otolaryngology under the direction of one of us (F. D. W.).

wise impermeable strictures have been successfully treated by the use of the biplane fluoroscope, but not all are amenable to this method.

For a limited group of cases in which these methods have failed on account of complete obstruction of the esophagus, we propose a double approach which has had some measure of success in our hands. It seems worth attempting in the difficult cases rather than to immediately condemn the patient to an artificial esophagus. In simple terms, it consists of guiding bougies through the area of stricture by external



Fig. 2.—Showing the threadlike stricture 2 cm long in the upper third of the esophagus on admission.

manipulation effected through surgical exposure of the esophagus at the strictured area, but without opening the esophagus. The bougies are passed either from above or below, or both. The method is, of course, more easily applicable in the cervical portion of the esophagus where surgical exposure is simplest, but there is no fundamental reason why it cannot be applied elsewhere in the esophagus. So far we have not had occasion to use the method on a simple stricture of the thoracic portion

of the esophagus although the exposure of the thoracic esophagus in a case of multiple stricture is now planned (Case 3).

The development of this method was the result of several experiences in surgery of the esophagus, in which sharp objects became impaled in the wall of the esophagus so that they could not be removed by means of the esophagoscope alone. We have been able, through external manipulation of the esophagus after surgical exposure, to dislodge them without opening the esophagus. They can then be successfully hauled through the esophagoscope. The method also recalls the familiar use of the esophagoscope in the surgical treatment of esophageal diverticulum. The present application of the principle was suggested by one of us (F. D. W.).



Fig. 3.—Complete stenosis one month later. The esophagus is dilated and atonic above the stricture. Complete stenosis seems to occur more rapidly under gastrostomy feeding and rest of the esophagus.

CASE 1.—(No. 161808.) Lye burn of the cervical esophagus. A 12-year-old negro boy accidentally swallowed lye five weeks before admission. He had been able to swallow nothing but liquids for the preceding two weeks, had lost weight, and had pain and difficulty in swallowing.

X-ray showed a marked stricture 2 cm. long in the upper third of the esophagus (Fig. 2). He was referred to the department of surgery for gastrostomy, which was performed in two stages, five days apart.

The wound was well healed in two weeks and feedings were carried out through the gastrostomy tube. An attempt to have him swallow a string was unsuccessful and it was impossible to pass a ureteral bougie through either the mouth or the gastrostomy. Since the patient was unable to swallow liquids by that time, four weeks after admission, another x-ray examination was made which showed no barium passing the stricture (Figs. 3 and 4). During the next three weeks, repeated attempts to pass a string or bougie from above or below were unsuccessful and it was therefore decided to employ external exposure.

He was operated upon Nov. 16, 1940, approximately seven weeks after admission and twelve weeks after the injury. The operative note is as follows:

— ...



Fig. 4.—The radiopaque ureteral bougie is turned back by the complete stricture, when approached from below.

"Under avertin and ether anesthesia an incision was made along the posterior border of the right sternocleidomastoid muscle. Dissection proceeded down to the esophagus, passing laterally and posteriorly to the carotid sheath. The esophagus was identified without difficulty. The esophagus appeared entirely normal to external inspection and examination, but did show some dimpling near the site of the stricture when a bougie was thrust against it. Repeated unsuccessful attempts were made to pass bougies of various materials, tensions, and degrees of sharpness. All important structures were packed off during this manipulation, which was done



slowly and carefully. In spite of every caution, a sharp pointed metal instrument passed through the wall of the esophagus out into the neck on three different occasions. A bougie was then passed through the gastrostomy opening by an assistant. The tip of the bougie which ascended the esophagus could be felt in close proximity to the tip of the bougie which descended from above. At times the two tips seemed to be only a few millimeters apart. It was, however, impossible to permeate the stricture from above or below, while the inferior bougie was in the hands of the assistant. The surgeon, therefore, grasped the esophagus with his left hand and manipulated the bougie from below through the gastrostomy with his right hand. In this way it was possible to guide the lower bougie much more accurately than had been possible previously by giving directions to the assistant. The lower bougie then presented such a clear and well defined prominence as seen from above through the esophagoscope that it was possible to incise the mucosa overlying the tip of the lower bougie and to allow it to pass freely into the upper esophagus. A string was then tied to the lower bougie and drawn down through the stricture and brought out through the gastrostomy. This entire procedure, guided by the fingers of the left hand of the surgeon, which encircled and manipulated the esophagus from the outside, was carried out with surprising ease considering the long drawn-out and futile attempts that had been made previously. At the conclusion there was no evidence of leakage from the three tiny perforations in the wall of the esophagus. However, sulfanilamide powder was sprinkled freely around the circumference of the esophagus, and a soft rubber drain was brought out at the lower angle of the wound. The incision in the neck was then closed loosely, using interrupted plain zero catgut for the buried sutures and interrupted fine silk for the skin. In spite of the prolonged operation, the boy went through it quite well."

Retrograde dilatation was started in a few days. The incision in the neck was healed in eleven days. The patient was discharged one month after operation, at which time the stricture had been dilated up to a caliber of 30 French.

CASE 2.—(No. 79526.) Spasm of cricopharyngeus muscle (?). A 73-year-old white woman had been having increasing difficulty in swallowing for the past two years. At the time of admission she was only able to swallow liquids, had lost twenty pounds and had frequent attacks of strangling and a sensation of fullness in her chest. Voice weakness and frequent expectoration were also present.

Complete physical examination was negative. Fluoroscopic examination of the esophagus was attempted the day after admission. The barium collected in a small pocket at the level of the upper border of the larynx and none entered the esophagus.

The following day esophagoscopy showed marked obstruction at the upper end of the esophagus. No lumen could be found, but the mucous membranes were normal. Since we suspected that we might have entered a diverticulum, the examination was discontinued and further x-ray studies were ordered.

The next day a lateral x-ray of the neck showed a definite rounded mass 5 mm. in thickness, compressing the posterior aspect of the trachea from the upper level of the larynx downward for 2.5 cm. (Figs. 5 and 6). When barium was swallowed, it stopped as before, but a small trickle entered the esophagus. The roentgenologist reported a tumor in the esophagus, pressing on the trachea.

An attempt to swallow a string the following day was unsuccessful, so a second esophagoscopy was done for the purpose of obtaining a biopsy. Again no mucosa changes were noted and we were unable to enter the esophagus. Several bits of tissue were removed for microscopic examination. The pathologic report showed benign scar tissue with normal overlying epithelium.

Because of this mass of conflicting evidence, we advised external exploration, which was done Aug. 27, 1940. The operative note is as follows:

"Under avertin and novocain anesthesia, an incision was made along the posterior border of the right sternocleidomastoid muscle. The dissection was carried down to the esophagus which was carefully dissected free from the surrounding structures. At no point could any evidence of diverticulum be seen, nor were any other abnormalities evident from an examination of the esophagus on the exterior. At this point the esophagoscope was again inserted in the hypopharynx, and by making traction on the edges of the incision in the neck, the esophagoscope passed easily



Fig 5—The mouth and pharynx are filled with barium, but none enters the esophagus

down into the lower portion of the esophagus. With the esophagoscope in place, a tube was inserted into the stomach. No reason for the obstruction could be determined, either by examining the esophagus from the outside, or by the examination through the esophagoscope on the inside. The patient stood the operation well. The wound was closed loosely, after dusting with sulfanilamide powder, using plain zero catgut for the deeper stitches and silk for the skin, leaving in place a small soft rubber drain at the lower angle of the wound."

She was given sulfanilamide by mouth for five days. Then the stomach tube was removed and soft diet started. She swallowed so well that a regular diet was given three days later which she also took without difficulty. As the neck wound had

slowly and carefully. In spite of every caution, a sharp pointed metal instrument passed through the wall of the esophagus out into the neck on three different occasions. A bougie was then passed through the gastrostomy opening by an assistant. The tip of the bougie which ascended the esophagus could be felt in close proximity to the tip of the bougie which descended from above. At times the two tips seemed to be only a few millimeters apart. It was, however, impossible to permeate the stricture from above or below, while the inferior bougie was in the hands of the assistant. The surgeon, therefore, grasped the esophagus with his left hand and manipulated the bougie from below through the gastrostomy with his right hand. In this way it was possible to guide the lower bougie much more accurately than had been possible previously by giving directions to the assistant. The lower bougie then presented such a clear and well-defined prominence as seen from above through the esophagoscope that it was possible to incise the mucosa overlying the tip of the lower bougie and to allow it to pass freely into the upper esophagus. A string was then tied to the lower bougie and drawn down through the stricture and brought out through the gastrostomy. This entire procedure, guided by the fingers of the left hand of the surgeon, which encircled and manipulated the esophagus from the outside, was carried out with surprising ease considering the long drawn-out and futile attempts that had been made previously. At the conclusion there was no evidence of leakage from the three tiny perforations in the wall of the esophagus. However, sulfanilamide powder was sprinkled freely around the circumference of the esophagus, and a soft rubber drain was brought out at the lower angle of the wound. The incision in the neck was then closed loosely, using interrupted plain zero catgut for the hurried sutures and interrupted fine silk for the skin. In spite of the prolonged operation, the boy went through it quite well."

Retrograde dilatation was started in a few days. The incision in the neck was healed in eleven days. The patient was discharged one month after operation, at which time the stricture had been dilated up to a caliber of 30 French.

CASE 2.—(No. 79526.) Spasm of cricopharyngeus muscle (?). A 73-year-old white woman had been having increasing difficulty in swallowing for the past two years. At the time of admission she was only able to swallow liquids, had lost twenty pounds and had frequent attacks of strangling and a sensation of fullness in her chest. Voice weakness and frequent expectoration were also present.

Complete physical examination was negative. Fluoroscopic examination of the esophagus was attempted the day after admission. The barium collected in a small pocket at the level of the upper border of the larynx and none entered the esophagus.

The following day esophagoscopy showed marked obstruction at the upper end of the esophagus. No lumen could be found, but the mucous membranes were normal. Since we suspected that we might have entered a diverticulum, the examination was discontinued and further x-ray studies were ordered.

The next day a lateral x-ray of the neck showed a definite rounded mass 5 mm. in thickness, compressing the posterior aspect of the trachea from the upper level of the larynx downward for 2.5 cm. (Figs. 5 and 6). When barium was swallowed, it stopped as before, but a small trickle entered the esophagus. The roentgenologist reported a tumor in the esophagus, pressing on the trachea.

An attempt to swallow a string the following day was unsuccessful, so a second esophagoscopy was done for the purpose of obtaining a biopsy. Again no mucosa changes were noted and we were unable to enter the esophagus. Several bits of tissue were removed for microscopic examination. The pathologic report showed benign scar tissue with normal overlying epithelium.

In 1941 she was asked to return to the hospital for a trial of the present method. Although her nutrition was good, she was willing to try anything that offered hope of swallowing in a normal manner. The esophagus was examined by fluoroscopy and the obstruction found to be still complete. Peroral esophagoscopy showed complete obstruction in the upper esophagus. We felt that passing a bougie up from the stomach offered the best chance of permeation, but since we were unable to identify the lower end of the esophagus by retrograde esophagoscopy, it was decided to open the abdominal wall for the purpose of guiding the bougie under finger manipulation. The operative note is as follows:



Fig. 7.—Showing a marked stricture in the upper third of the esophagus, with barium entering the lower esophagus. Fluoroscopic examination showed a second stricture in the lower third, not shown in this film. This was the condition on admission in 1930.

“Under spinal anesthesia a high upper abdominal incision was made and the peritoneum opened. The lower end of the esophagus between the diaphragm and the stomach was found without difficulty, and after numerous attempts, a stiff bougie was finally apparently directed into the esophagus. After this was accomplished, the incision in the abdominal wall was closed in layers, using plain zero catgut for the peritoneum, chrome zero catgut for the superficial fascia, and silk for the skin.

“The patient was then taken to the fluoroscopy room and the bougie examined under the fluoroscope. Unfortunately, it was found that the bougie could not be made to pass further up the esophagus than the level of the diaphragm. There

healed she was discharged several days later, eating normally, and has had no further trouble.

It is believed that we were dealing with a marked spasm of the *cricopharyngeus* with perhaps some psychogenic factors in addition. The method employed appears to have been the safest and surest way to relieve her symptoms and to definitely rule out diverticulum and tumor.



Fig. 6.—A lateral view of the neck shows an apparent esophageal tumor, compressing the trachea.

CASE 3.—(No. 83192.) Multiple lye burns of esophagus, upper and lower thirds.

A 27-year-old woman was admitted in June, 1930, with a history of having intentionally swallowed a large amount of lye nine months previously. She was then subsisting entirely on liquids, in small amounts, and had lost considerable weight.

X-ray examination on admission showed a marked stricture high in the upper third and another stricture in the lower third (Fig. 7), and immediate gastrostomy was done. Repeated attempts at permeation both from above and below were unsuccessful, and x-ray two months after admission showed complete occlusion (Fig. 8).

She was sent elsewhere for an attempt at permeation under the biplane fluoroscope. Since this procedure was unsuccessful after repeated attempts, she was sent home to follow a gastrostomy life. She learned to chew her meals and expectorate them into the funnel of her gastrostomy tube; thereby she was able to maintain her nutrition and to carry out the normal obligations of life. Two year later, in 1932, she was again examined, but no opening could be found and she returned home to resume her unhappy existence.

sulfanilamide powder was sprinkled around the circumference of the esophagus and a soft rubber drain was brought out at the lower angle of the wound. The incision in the neck was closed rather loosely, using interrupted plain zero catgut for the buried sutures and interrupted fine silk for the skin."

The result of these procedures in this patient have failed and she is again leading her gastrostomy life. It should be noted in this case that it was possible to approach each stricture from only one side. The permeation of the stricture is undoubtedly facilitated by approaching it from above and below simultaneously.

#### DISCUSSION

In two out of three difficult cases of esophageal obstruction which had not yielded to other methods, it was possible through exposure of the esophagus to effect the establishment of a new lumen. In the third case the method failed because of multiple strictures of the organ. In view of the great difficulty attendant upon the treatment of these impermeable cases, it has seemed worth while to present this method of approach.

At the present time it is planned to develop the principle one step further in a final attempt to relieve the patient described in Case 3. Through a transthoracic esophagostomy, bougies will be passed both upward and downward. At the same sitting, attempts will be made to incise the strictures, if possible, through the esophagoscope passed respectively by mouth and by gastrostomy. It is considered safe to open the esophagus under these conditions inasmuch as it has been completely occluded over a period of twelve years. It is possible, of course, that either complete fusion of its wall or additional strictures will be encountered which will, of course, completely prevent the success of this plan of approach. In that event, this patient is an ideal case for the construction of antethoracic esophagus.

#### CONCLUSION

External exposure of the esophagus is advocated as a safe surgical procedure to aid in the passage of bougies for the permeation of complete esophageal strictures, in selected cases, when other methods have failed.

seemed to be no doubt that the bougie was actually in the lower end of the esophagus while the operator's hand was inside the peritoneal cavity. The patient went through this lengthy manipulation in good condition."

The abdominal wound soon healed, so we decided to try permeation from above. After two months at home she returned for this attempt.



Fig. 8.—Complete stenosis two months later. As in Fig. 3, the esophagus is dilated and atonic above the stricture. Again, gastrostomy feeding and rest of the esophagus seem to favor the development of complete stenosis.

On May 9, 1941, the upper esophagus was exposed. The operative note is as follows:

"Under avertin and ether anesthesia, an incision was made along the posterior border of the right sternocleidomastoid muscle. The esophagus was approached by retracting the carotid sheath medially. It was carefully freed from a point above and below the thoracic entrance upward to its junction with the posterior pharynx. Again there was no external evidence in the esophageal wall of the known stricture.

"Various bougies were then passed down the esophagus and manipulated by the fingers of the surgeon in an attempt to guide the instrument down the lumen of the esophagus. After about one hour of manipulation with various types and sizes of instruments, the procedure was abandoned because it was quite impossible to penetrate the stricture. It is felt that had it been possible to pass the bougie upward from below, it might have been possible to penetrate this stricture. At no time was there any evidence of perforation of the esophagus. However, a small amount of

patients under 40 years of age. Eighteen cases, or 9 per cent, occurred in patients past the age of 70. The three decades from 40 to 70 have approximately the same incidence. It is interesting that sixteen patients, or 8 per cent, were under 40 years of age, but as will be shown subsequently, a fair percentage of patients over 40 years of age would have fallen into this group had they sought treatment immediately following the appearance of the first symptom. Therefore, it is important to stress that a routine examination of the female breast in women under the age of 40 is as essential as it is in women above this age. The old adage that any mass in the breast of a woman past 40 years of age be considered malignant leaves one with a false sense of security, and should be revised to state that regardless of the patient's age, a mass in the female breast cannot be considered benign until definitely proved so by histologic evidence.

TABLE II  
PREGNANCIES

NUMBER OF PREGNANCIES	NUMBER OF CASES	PER CENT
None	70	36.3
Single	24	12.4
Multiple	99	51.3
Total	193	

Table II deals with pregnancies in relation to the 193 cases of cancer of the breast studied. In seventy cases, or 36 per cent, there were no pregnancies. In twenty-four cases, or 12 per cent, a single pregnancy was recorded. In ninety-nine cases, or 51 per cent, multiple pregnancies occurred. From this small series no deduction can be drawn relative to the influence of gestation on the incidence of cancer in the female breast.

The three primary symptoms were mass in 176 cases, or 91 per cent; pain in thirteen cases, or 7 per cent; and nipple discharge in four cases, or 2 per cent, as seen in Table III. Careful attention should be called

TABLE III  
FIRST SYMPTOM

NUMBER OF CASES	MASS		PER CENT		PAIN	PER CENT	NIPPLE DISCHARGE	PER CENT
193	176		91.2		13	6.7	4	2.0
	Discovered by patient	Per cent	Discovered by doctor	Per cent				
	171	97.1	5	2.8				

to the 176 patients who presented themselves with a mass in the breast as their first symptom. One is struck by the fact that in 171 instances the patient was fully aware of the mass in her breast prior to the seeking



## CARCINOMA OF THE BREAST

SAMUEL J. STABINS, M.D., AND ANDREW H. DOWDY, M.D.,  
ROCHESTER, N. Y.

(From The Tumor Clinic of Strong Memorial Hospital and The School of Medicine  
and Dentistry, University of Rochester)

IT IS the feeling of the authors that the radical surgical treatment of cancer of the breast is well standardized. Any further improvement in technique may add to the patient's comfort, but very little improvement in clinical results can be expected from this type of treatment. It is likewise the feeling of the authors that sufficient attention has been paid to the patients who have lived five years or more free of the disease, but that too little emphasis has been given those who fail to survive this period. Often we can profit as much, if not more, from an analysis of our failures. We feel that our five-year end results will not vary markedly from those of other clinics. Consequently, no attempt will be made to review the abundant literature which deals with a purely statistical analysis of five-year survivals. This study, therefore, was undertaken for the purpose of evaluating the various factors which may influence the disease prior to the institution of treatment.

One hundred and ninety-three cases of cancer of the female breast occurring between the years of 1926 and 1936, and followed in our tumor clinic, are the basis of this study. Of this total, 156 patients were subjected to a radical mastectomy in our clinic. Of the remaining thirty-seven patients, fifteen were subjected to a simple mastectomy, ten received radiation only, and in twelve the treatment was done elsewhere and it was impossible to ascertain sufficient data.

TABLE I  
DISTRIBUTION OF CASES BY DECADES

DECADE	NUMBER OF CASES	PER CENT
20-30	2	1.0
30-40	14	7.2
40-50	52	26.9
50-60	59	30.6
60-70	48	24.9
70-80	14	7.2
80-90	4	2.0
Total	193	

Table I deals with the distribution of these cases by decades. One hundred and fifty-nine cases, or 83 per cent, occurred in patients between the ages of 40 and 70. Sixteen cases, or 8 per cent, occurred in

and one within two years. It is interesting to note that of the seventy-four patients seen within three months after the recorded onset of symptoms, twenty-four, or 32 per cent, were found to have histologic involvement of the axillary nodes. It seems more probable that the initial symptom in these twenty-four cases was of a longer duration.

In view of the afore-mentioned, a study was made to determine the five-year end result in relation to the duration of the first symptoms (Table V). Of the seventy-four patients with a duration of the present-

TABLE V  
FIVE-YEAR END RESULT IN RELATION TO THE DURATION OF THE FIRST SYMPTOM

DURATION OF PRESENTING SYMPTOM	NUMBER OF CASES	NUMBER OF PATIENTS ALIVE AND WELL 5 YEARS LATER	PERCENTAGE WELL 5 YEARS LATER
Less than 3 months	74	30	40.5
3 months to 1 year	41	13	31.7
Over 1 year	78	16	20.5
Total	193	59	30.6

ing symptom less than three months, thirty, or 40.5 per cent, were alive and well five years later; of the forty-one patients with the duration of the presenting symptom three months to one year, thirteen, or 31.7 per cent, were alive and well five years later; and of the seventy-eight patients with the presenting symptom of one year or longer, sixteen, or 20.5 per cent, were alive and well five years later. Of the total of 193 cases, 59, or 30.6 per cent of the patients were alive and well five years later. On the basis of these findings, it would seem that the best results are obtained in those patients with the shortest positive history, and as the time interval between the initial symptom and the seeking of medical advice is increased, the prognosis for a five-year arrest of the disease is reduced.

TABLE VI  
QUADRANT LOCATION OF TUMOR

QUADRANT	NUMBER OF CASES	PER CENT
Outer half	122	63.2
Inner half	31	16.1
Center	32	16.6
Not obtainable	8	4.1
Total	193	

The location of the tumor by quadrant is represented in Table VI. One hundred and twenty-two cases, or 63 per cent, occurred in the outer half; thirty-one, or sixteen per cent, in the inner half; and thirty-two, or 16 per cent, in the central portion of the breast. In eight cases the location of the mass was not recorded. In Table VIII an analysis of the end results by quadrant location is recorded in the 156 cases in which the

of medical advice. Only in five instances was the doctor able to find a mass in the breast without the patient having had previous knowledge of its presence. In a number of instances when the patient presented herself complaining of a "lump" in the breast, the doctor on his first examination was unable to confirm its presence, and it was only after repeated examinations involving a valuable loss of time to the patient that the doctor was able to confirm the presence of such a mass. One cannot overemphasize the fact, therefore, that whenever, a woman presents herself complaining of a lump in the breast, serious consideration should be given to such a complaint. If on the first examination this symptom is not substantiated, it behooves the examiner to make repeated examinations. There are some women who fall into a classification of "hysterical breasts," but this number is comparatively small and one should hesitate to label any woman in this way. As a rule it is not difficult to identify this type of individual. Careful history taking will bring out the fact that the patient is of an unstable, psychogenic personality, and in addition has been overexposed to cancer propaganda.

The second most frequent symptom was pain, and occurred as the first symptom in thirteen cases, or 7 per cent, and was usually of the radiating type. This re-emphasizes the fact that pain is not an early symptom of carcinoma of the breast. Nipple discharge occurred as the primary symptom in only four cases, or 2 per cent. The duration of the first symptom (Table IV) is of interest and probably has some bearing upon the ultimate prognosis of cancer of the breast.

TABLE IV  
DURATION OF FIRST SYMPTOM IN 193 CASES

SYMPTOM	NUMBER OF CASES	LESS THAN 3 MONTHS	PER CENT	3 MONTHS TO 1 YEAR	PER CENT	OVER 1 YEAR	PER CENT
Mass	176	64	36.4	40	22.7	72	40.9
Pain	13	8	61.5	0		5	38.5
Nipple discharge	4	2	50.0	1	25.0	1	25.0
Total	193	74	38.3	41	21.2	78	40.4

Sixty-four cases out of 176, or 36.4 per cent, were recorded as having had the lump less than three months. Forty cases, or 22.7 per cent, were recorded as having had the lump three months to one year, and seventy-two cases, or 40.9 per cent, were recorded to have had the lump over one year.

Of the thirteen patients who presented themselves with pain as the initial symptom, eight, or 61.5 per cent, were seen within three months of the onset, and five were seen one year or later after the onset. Of the four patients who complained of discharge from the nipple as the first symptom, two were seen within three months, one within six months,

This is especially so in those cases without axillary metastases. The worst prognosis seems to be in those patients with proved axillary metastases in which the primary tumor was located either in the inner half or the center of the breast.

Aside from the disease itself, elephantiasis has been one of the most troublesome complications. Two hundred and ninety-eight cases followed between the years of 1926 and 1941 were studied from this standpoint (Table IX). Of this total, ninety patients, or 30.2 per cent, developed elephantiasis following radical mastectomy. We did not consider any case as being satisfactory for this group unless there was a persistent increase in the circumference of the affected arm one inch more than that of the contralateral side. No attempt was made to evaluate the patient on a functional basis of the arm. It was felt that the cases should be studied to determine if the involvement of the axillary glands was a factor in the incidence of elephantiasis. In 167 cases, or 56.3 per cent, such involvement was shown. We could find no appreciable difference in the incidence of the elephantiasis between the group showing positive axillary nodes and the group which did not.

TABLE IX  
ANALYSIS OF ELEPHANTIASIS IN 298 CASES  
(1926-1941)

		PER CENT
Total number of cases	298	
With elephantiasis	90	30.2
Without elephantiasis	208	69.8
Total number with positive nodes	167	56.3
With elephantiasis	55	32.9
Without elephantiasis	112	67.1
Total number with negative nodes	131	43.7
With elephantiasis	35	26.7
Without elephantiasis	96	73.3

Further analysis reveals that in forty-nine cases involving radical mastectomy, the operation was supplemented by a skin graft procedure

TABLE X  
ANALYSIS OF ELEPHANTIASIS IN 49 CASES WITH SKIN GRAFT

		PER CENT
Total number with skin graft	49	
With elephantiasis	10	20.4
Without elephantiasis	39	79.6
Total number with positive nodes	28	57.1
With elephantiasis	6	21.4
Without elephantiasis	22	78.6
Total number with negative nodes	21	42.9
With elephantiasis	4	19.0
Without elephantiasis	17	81.0

patients were subjected to radical mastectomy. Table VII is included to indicate the type of treatment accorded the 193 cases.

TABLE VII  
CLASSIFICATION ACCORDING TO TREATMENT

TYPE OF TREATMENT	NUMBER OF CASES	PER CENT
Radical mastectomy	156	80.5
Simple mastectomy	15	7.8
Radiation only	10	5.2
Insufficient data	12	6.2
Total	193	

The end results in the 156 patients subjected to a radical mastectomy were studied from the standpoint of the location of the primary tumor with and without proved axillary metastases. Of the total of the eighty-six cases involving proved axillary metastases, the primary tumor was located in the outer half of the breast in fifty-six patients. Twenty, or 35.7 per cent, were alive and well at the end of five years. In twelve instances the primary tumor was in the inner half of the breast, and only one, or 8.3 per cent, was alive and well at the end of five years. Of the eighteen patients with the tumor located in the center of the breast, three, or 16.6 per cent, were alive and well after five years. Twenty-four patients, or 27.9 per cent, represent the five-year survivals in the group of eighty-six with proved axillary metastases. Seventy cases without axillary metastases were studied from a survival viewpoint. Forty-three occurred in the outer half, and twenty-three patients, or 53.4 per cent, were alive and well five years later. Thirteen occurred in the inner half, and six patients, or 46.1 per cent, were alive and well five years later. Fourteen occurred in the center of the breast, and six patients, or 43 per cent, were alive and well five years later. Of the total of seventy cases, thirty-five patients, or 50 per cent, were alive and well five years later, as seen in Table VIII.

TABLE VIII  
156 CASES OF RADICAL MASTECTOMY  
END RESULTS

LOCATION OF PRIMARY TUMOR	WITH PROVED AXILLARY METASTASES			WITHOUT AXILLARY METASTASES		
	NUMBER OF CASES	NUMBER OF 5-YEAR SURVIVALS	PER CENT OF 5-YEAR SURVIVALS	NUMBER OF CASES	NUMBER OF 5-YEAR SURVIVALS	PER CENT OF 5-YEAR SURVIVALS
Outer half breast	56	20	35.7	43	23	53.4
Inner half breast	12	1	8.3	13	6	46.1
Center of breast	18	3	16.6	14	6	43.0
Total cases	86	24	27.9	70	35	50.0

It would seem from Table VIII that the best chance for a five-year survival is in the patient who has a tumor in the outer half of the breast.

## CONCLUSIONS

1. Clinical end results in cancer of the breast seem to bear a relationship to the duration of the initial symptom.
2. Too long an interval exists between the patient's awareness of the initial symptom and the institution of treatment.
3. Skin grafting is a definite factor in the reduction of the incidence of elephantiasis.
4. Skin grafting is no assurance against local recurrences.
5. Skin graft should be placed in the apex of the axilla. Otherwise it does not fulfill its function of doing away with the dead space.

From these studies it would appear that cancer of the breast occurs much more frequently in women under 40 years of age than is generally appreciated. Likewise, it has been shown that the patient is in a position to recognize the early symptoms and signs which indicate abnormality of the breast. Furthermore, it was found that the percentage of five-year survivals was highest in those patients with the initial symptom of less than three months' duration. The five-year survival in this group is 40.5 per cent. With the increase in the duration of the presenting symptom from three months to one year, 31.7 per cent were alive, and in the group over one year the percentage had dropped to 20 per cent. From these findings it would seem that there is room in the field of preventive medicine on the part of the practitioner to stress to his patient the importance of seeking medical advice as soon as the abnormality is noted. When the tumor is located in the outer half of the breast the chance of a five-year survival was greater than in any other location. When the tumor was not in the outer half, and it was found at operation that the axillary nodes were involved, the prognosis for a five-year survival was extremely poor.

From the study of 298 cases relative to elephantiasis, it was found that a skin graft was of definite value in decreasing the incidence of elephantiasis. Although the difference is not striking in our series, we are certain that there would have been a greater disproportion if the skin graft had been more complete. Halsted stressed the importance of leaving the wound open and placing the grafts high in the axilla to avoid tension and contracture. In some of our cases it was apparent from the operative note that the skin grafting failed to accomplish this. If the graft is not placed in the apex of the axilla, it fails to accomplish the purpose of obliteration of the dead space. We have observed local recurrences in a number of the skin grafts, and it is our feeling that skin grafting plays a very little part in decreasing the incidence of such recurrences.

## CONCLUSIONS

1. Clinical end results in cancer of the breast seem to bear a relationship to the duration of the initial symptom.
2. Too long an interval exists between the patient's awareness of the initial symptom and the institution of treatment.
3. Skin grafting is a definite factor in the reduction of the incidence of elephantiasis.
4. Skin grafting is no assurance against local recurrences.
5. Skin graft should be placed in the apex of the axilla. Otherwise it does not fulfill its function of doing away with the dead space.



# WHIPPLE'S DISEASE, OR INTESTINAL LIPODYSTROPHY

HERMAN E. PEARSE, M.D., ROCHESTER, N. Y.

(From the Department of Surgery, the University of Rochester, School of Medicine and Dentistry)

WHIPPLE, in 1907, described a disease which was "characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues," and which he termed *intestinal lipodystrophy*. This disorder caused loss of weight to the point of emaciation; loss of strength; microcytic anemia; recurrent arthritis; doughy swelling of the abdomen associated with tenderness and gaseous distention; and fatty diarrhea with an average of three or four stools a day, which were light or clay colored and consisted of over 50 per cent fat and fatty acids, by weight. There was no interference with fat splitting for the fat in the stool was almost completely composed of split fats and soaps in crystalline form.

Blumgart reported three cases of malabsorption of fat "which were not in accord with any hitherto recognized diagnosis, and which, because of similar signs, symptoms, course and postmortem findings, strongly suggested a definite disease entity." He states, "It would seem that a definite clinical and pathological syndrome with such an intangible etiologic background must have been previously recognized. Nevertheless, search of the literature has uncovered only one analogous case, reported by G. H. Whipple."

In 1936, Jarco reported a case of steatorrhea with unusual intestinal lesions which he felt had "great clinical similarity and virtual anatomical identity" with that described by Whipple.

The most recent description of this condition is by Reinhart and Wilson, who report a case of malabsorption of fat that was considered to be identical with those mentioned above. They compared the histologic slides of this case with those of Whipple and Jarco and felt that "the anatomical lesions were of the same basic type."

The case herein reported is considered to be of this group and is the seventh case described. It is the first in which the diagnosis was made during life, which permitted metabolic studies and observations on the effect of treatment. The true nature of the condition in this case was not established until Whipple examined the material removed at operation and made the diagnosis.

## REPORT OF CASE

H. B. (No. 158533, S. M. H.), a 59-year-old farmer, dates his present illness to fifteen years ago when he began having attacks of right upper quadrant abdominal

Presented at the meeting of the Society of University Surgeons, Cincinnati, Ohio, Feb. 12-14, 1942.

pain of a colic-like nature associated with nausea, vomiting, and jaundice. The pain occasionally radiated to the right shoulder, was aggravated by fatty food, and was relieved by bed rest. These attacks have not varied in frequency or severity in the intervening years but have continued more or less independently of his other complaints.

Thirteen years ago he began having pain, stiffness, and limitation of motion of the joints, particularly of the hands and knees. These arthritic symptoms were severe for eight years and subsided somewhat after the extraction of his teeth.

For the past two years he has had recurrent bouts of abdominal distention, associated with an intermittent crampy pain, and with diffuse tenderness of the abdomen. At times he has vomited large amounts of green fluid and at other times has retained ordinary food though his intake has been below normal. These recurrent attacks of abdominal pain and distention became so numerous and so severe that he was admitted to the Batavia Hospital in March, 1939, where a partial obstruction of the sigmoid colon was found. The symptoms of pain, vomiting, and abdominal distention became worse and he was operated upon June 3, 1939, at which time release of adhesions and a biopsy were done. The pathologic report of the tissue removed was "chronic inflammation."

Since there was little or no improvement after this operation, he was referred here on Oct. 20, 1939. Examination showed a chronically ill, white male of 59 years of age, who had pallor of the oral mucous membrane, no teeth, a lemon yellow tint to the skin, and no glandular enlargement. The lungs were clear, the right diaphragm was a little high, and the heart was enlarged to the left with a soft systolic apical murmur. The cardiac rhythm was fundamentally regular but ventricular extra systoles were occasionally present. There was peripheral arterio sclerosis with a blood pressure of 128/80 mm. Hg. The extremities showed arthritic changes but no edema.

Examination of the abdomen revealed marked gaseous distention associated with generalized tenderness most marked in the left lower quadrant. The abdomen had a peculiar consistency best described as "doughy," for resistance was felt without the presence of muscle spasm. No free fluid could be demonstrated. It was thought that multiple masses were present but they could not be certainly defined because of the gaseous distention. When x ray examination showed partial intestinal obstruction, operation was advised and done on Oct. 23, 1939.

When the abdomen was opened it was found that all the viscera were matted together in one solid mass. After adhesions were freed the loops of the intestine were seen to be bound together by a gelatinous appearing substance which, when released, was found to be a clear fluid. The intestinal loops were red, granular, and covered with a shaggy exudate. There were hard, pale pink nodules in the liver and on the intestines, omentum, and parietal peritoneum. This picture was unlike pseudomyxoma peritonei or colloid carcinomatosis in that the colloid appearing substance became fluid on its release and the nodules when cut were found to be hollow cysts containing a yellow oily substance. Several of these nodules were removed for histologic examination, many adhesions were released and the abdomen closed.

The patient made an uneventful convalescence from this operation. The report on the tissue removed states that many large phagocytic cells with foamy cytoplasm and many giant cells were present in a connective tissue stroma surrounding cystic areas. Special stains showed these foam cells and giant cells to be loaded with fat droplets. When the sections were shown to Dr G H Whipple, he made the diagnosis of intestinal lipodystrophy and stated that the lesions were the same as those he had described previously. This authoritative confirmation of the diagnosis gave confidence in proceeding with laboratory and metabolic studies, for this case was unique in that the diagnosis had been made during life.

The patient was discharged on a low fat diet and bile salts (sodium taurocholate 0.5 Gm. three times daily). Soon after his discharge from the hospital he began having abdominal pain which originated in the right upper quadrant and radiated

TABLE I  
LABORATORY FINDINGS

Urine		Blood Chemistry	
Albumin	0	Chlorides	585-595
Sugar	0	N.P.N.	25- 35
Mic.	Negative	Icterus index	6
Blood		CO <sub>2</sub> comb. P.	50%
W.B.C.	7,700-9,100	Amylase	80-140
Hb.	11.0-12.5-14 Gm.	Serum albumin	4.25
R.B.C.	4,030,000-4,730,000	Serum globulin	1.65
Differential		Total protein	5.90-6.8
Neutrophiles	85%	Calcium	9.1
Lymphocytes	12%	Phosphorus	4
Eosinophiles	2%	Phosphatase	3.2 (Bodansky units)
Monocytes	1%		
Smear		Blood Fats	
Few microcytic	R.B.C.	Phospholipid	Cholesterol
Retiuloocytes	1.4%	No. 1	268
Blood group	A	No. 2	310
Wassermann	Negative		
Glucose Tolerance Test		Fluid in Intra-abdominal Nodules	
	11/13/39	Fatty acids	74%
	3/13/41	Cholesterol	12.5%
Fasting	72 mg. %	Phospholipid	2.06%
½ hour	114 mg. %		
1 hour	123 mg. %		
1½ hour	127 mg. %		
2 hour	87 mg. %		
3 hour	62 mg. %		

through to the back in the intrascapular region. This persisted and he was re-admitted to the hospital two months after his discharge. The findings led to a

TABLE II  
Vitamin A Absorption—7000 I.U. Vitamin A per Kilogram

BEFORE TREATMENT (11/5/39)		AFTER TREATMENT—BILE SALTS (3/13/41)	
Fasting	30	39 units per 100 c.c.	
2 hours		39 units per 100 c.c.	
4 hours		36 units per 100 c.c.	
6 hours	108	110 units per 100 c.c.	
8 hours		548 units per 100 c.c.	
12 hours	291	402 units per 100 c.c.	
Carotene	14	50 units per 100 c.c.	
Xanthophyll	25	77 units per 100 c.c.	

Metabolic Studies After Bile Salts—Diet Contains 100 Gm. Fatty Acid

STOOL		
	BEFORE TREATMENT (11/2/39)	AFTER BILE SALTS (3/13/41)
	Pale, creamy, foul, guaiac negative	Brown, formed, guaiac negative
	59.5%	25%
Lipid-dry stool	44.2%	20%
Split fat	12.2%	
Neutral fat	3.1%	5%
Unsaponifiable		

diagnosis of cholecystitis, which was confirmed by intravenous cholecystogram, but because of his poor condition operation was deferred and he was discharged. He returned one month later, stating that the attacks of pain had become more frequent and severe and were now associated with profuse vomiting. It was thought possible that the cholecystitis was a factor influencing the lipodystrophy; cholecystectomy was advised.

Operation was done Jan. 4, 1940, at which time the right upper quadrant of the abdomen was freed of the adhesions that had prevented its inspection at the previous laparotomy. Large masses of the cystic nodules were on the under surface

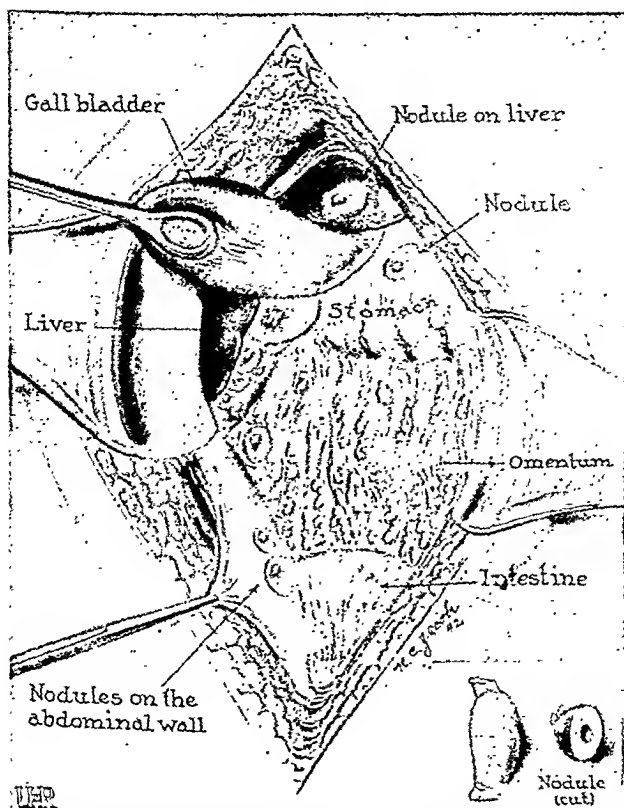


Fig. 1.—The appearance of the abdominal viscera in Whipple's disease, as seen at the second operation. Many adhesions were freed before this view was obtained. In the insert, one of the nodules is cut to show its hollow center.

of the liver on either side of the gall bladder (Fig. 1). Several of these were removed and the gall bladder was excised. He recovered satisfactorily from this operation and was sent home on a low fat diet, sodium taurocholate, calcium, and vitamin A. He improved remarkably, gained weight and strength, and was able to return to work. One year later he was readmitted to the hospital for metabolic studies consisting of vitamin A and fat absorption tests on a diet containing 100 Gm. of fatty acid. The results are shown in Table II, where it will be seen that in comparison to the data of November, 1939, there is a great improvement in the absorption of fat. This was obtained after prolonged, continuous administration of bile salts and it was decided to discontinue this medication to determine the result. Shortly after this, symptoms of indigestion, nausea, gas, and diarrhea

occurred. Bile salts were resumed and the symptoms disappeared. This was tried a second time with the same result, therefore the patient was instructed to continue indefinitely on bile salt medication. He is now well.

#### DISCUSSION

The pathologic changes in intestinal lipodystrophy as originally given by Whipple may well be repeated here, for nothing can be added to that description. He says: "The villi of the small intestine are enlarged by deposits of osmic acid reducing bodies (neutral fats and fatty acids). Such deposits are most numerous in the glands, but alike in all these situations. They are of all sizes from minute grains, intra- or extra-cellular in location, up to huge irregular droplets and there is the greatest variety of forms. Many of the larger masses show rosettes of fatty acid crystals and they may occupy spaces which are lined by endothelium suggesting dilated lymph channels. The majority of the larger deposits are outlined by polynuclear giant cells or large mononuclear cells of polyblastic type which in some instances seem to be eroding the fatty material and are closely applied to its edge. The epithelium of the *mucosa* is normal as far as the microscope shows. The interglandular stroma contains about the usual number of lymphocytes, plasma cells, and eosinophiles, but there is an infiltration with great numbers of polyblasts—large mononuclear, amoeboid cells with pink granular protoplasm. A second type of cell which is very conspicuous has an abundant foamy protoplasm, a pale vesicular nucleus and is actively amoeboid; this may be a type of polyblast. Ecchymoses are numerous wherever we find the fatty deposits. The submucosa shows invasion with great numbers of these polyblastic cells especially about the fat deposits which in some places are abundant, in others absent. There may be a very definite eosinophilia in such areas. The *glands* show the most extensive changes, especially the larger ones. In some the lymphatic nodules and cords are quite intact, the process seeming to begin in the sinuses of the glands with invasion of the characteristic cells and small irregular fat deposits. The next stage is an invasion by fibroblasts and capillaries with more or less extravasation of blood, increase in size and number of the fat deposits and distortion of the gland architecture. The large mononuclear cells increase rapidly in numbers and giant cells become conspicuous. The final stage shows a very large gland packed with fat deposits of all sizes and shapes, whose stroma is made up of dense fibrous tissue full of ecchymoses and great numbers of giant and mononuclear cells."

The oily substance in the cystic nodules was found to be 74 per cent fatty acid (Table II). It is probable that this nodular lesion results from a protective fibroplastic reaction around fat that is liberated within the peritoneal cavity.

The response of this patient to bile salt administration suggests that the disorder may be due to a fault in bile salt metabolism. Unfortunately, quantitative tests are not available to determine the level of bile

salts in the blood so an analytical study of their metabolism is not possible. When bile salts are given in adequate dosage the patient's symptoms disappear, vitamin A absorption improves, and the fat content of the stool approaches normal. The symptoms return if bile salt administration is stopped and are relieved with resumption of treatment. Another significant fact is that much of the fat is split into fatty acids so that the fault present in the disease is apparently connected with abnormal absorption and utilization of fat.

These facts point to a disturbance of bile, particularly the bile salt metabolism which appears to be deficient. Whether this lack is caused by a faulty production or by abnormal loss of the bile salts cannot be determined, nor can it be proved by analytic studies that this hypothesis of the etiology is correct. But for the present, at least, this concept gives a satisfactory working basis for the management of the disease.

#### SUMMARY

1. Whipple's disease or intestinal lipodystrophy is characterized by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues, the matting together of the abdominal viscera, and the formation of hard nodules containing lipids in the liver and on all of the peritoneal surfaces.

2. The disease causes loss of weight to the point of emaciation, loss of strength, microcytic anemia, recurrent arthritis, doughy swelling of the abdomen associated with tenderness and gaseous distention, and fatty diarrhea.

3. The disorder is important surgically because it may be confused with gall bladder disease, intestinal obstruction, or carcinomatosis. The latter condition is suggested by the finding of a colloid-appearing substance and the presence of hard, pale pink nodules which resemble the lesions of metastatic carcinoma. Thus, a hopeless prognosis may be given whereas actually the outlook is favorable with adequate treatment.

4. Analytic data are presented which suggest that the abnormal fat digestion present in the disease is due to a fault in bile salt metabolism. This view is strengthened by the clinical response to bile salt administration but it cannot be proved until suitable analytic methods are available.

I am indebted to Dr. S. H. Bassett, Dr. W. R. Bloor, and Dr. A. B. McCoord for their cooperation in making the analytical chemical studies.

#### REFERENCES

1. Whipple, G. H.: A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissue. *Bull. Johns Hopkins Hosp.* 18: 382, 1907.
2. Blumgart, H. L.: Three Fatal Adult Cases of Malabsorption of Fat, *Arch. Int. Med.* 32: 113, 1923.
3. Jarco, Saul: Steatorrhea With Unusual Intestinal Lesions, *Bull. Johns Hopkins Hosp.* 59: 275, 1936.
4. Reinhart, H. L., and Wilson, S. J.: Malabsorption of Fat (Intestinal Lipodystrophy of Whipple), *Am. J. Path.* 15: 483, 1939.
5. Sailer, S., and McGann, R. J.: Lipophagic Granulomatosis of the Enteric Tract *Am. J. Digest. Dis.* 9: 55, 1942.

## SURGICAL TREATMENT OF SPASMODIC FACIAL TIC

WILLIAM J. GERMAN, M.D., NEW HAVEN, CONN.

(From the Department of Surgery, Yale University School of Medicine)

VERY little concerning facial spasm has been written in the American literature during the past five years. Two significant papers on the subject appeared in 1937. Howe, Tower, and Ducl<sup>2</sup> reported the appearance of fibrillary motor overflow in the muscles of the face after facial nerve regeneration following nerve section in monkeys. They ascribed this to axonal branching during nerve regeneration. This type of fibrillary motor overflow is seen, not infrequently, after recovery from Bell's palsy.

Coleman<sup>1</sup> was able to obtain satisfactory relief of severe tonic and clonic facial spasm, at the cost of partial facial paralysis, by section and resuture of primary facial nerve branches. Recurrent spasm appeared in six to twelve months. More lasting relief was obtained by complete section of the facial nerve, with hypoglossal anastomosis. The results of hypoglossal anastomoses are not ideal but are preferable to complete facial paralysis. Temporary relief of facial spasm was also obtained by alcohol injection of the facial nerve at the stylomastoid foramen, again at the cost of facial paralysis.

Facial spasm may be tonic in type, sometimes a sequela of encephalitis. More common is the clonic type; idiopathic, paroxysmal spasms, provoked by eating, talking, smoking, or emotional tension. It is more common in women, middle-aged to elderly. The muscles most frequently involved are the orbicularis oculi, the zygomaticus, and risorius, but minor or major spread to the other facial muscles, even the platysma, is common. The spasm is occasionally bilateral. The incidence of facial spasm is much less than that of trigeminal neuralgia, and somewhat greater than that of glossopharyngeal neuralgia.

The therapeutic objective is obvious: relief of spasm without paralysis of the face. So far this has not been attained. In some respects the problem is similar to that of trigeminal neuralgia. It is a common experience in this latter condition that incomplete root section or alcohol injection may be followed by satisfactory relief of pain without complete loss of sensation in the involved area. It appeared possible that a similar situation might obtain in the case of the facial nerve. The present operation was designed on this basis.

Presented at the meeting of the Society of University Surgeons, Cincinnati, Ohio, Feb. 12-14, 1942.

The surgical procedure, done under local anesthesia, is carried out through a vertical incision just anterior to the ear. The dissection is directed anteriorly along the parotid fascia to the anterior border of the parotid gland (Fig. 1), and the primary branches of the facial nerve are identified at this point. The several primary branches are then stimulated electrically, with the face sufficiently exposed to identify the functional destination of each branch. Those branches which, upon stimulation, cause contraction of those muscles especially involved in the facial

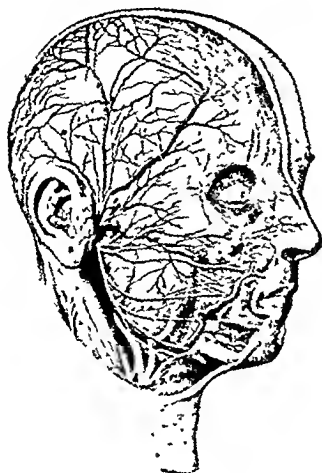


Fig. 1.—Anatomic relations of the facial nerve. The parotid gland has been divided to demonstrate the primary branches of the nerve.

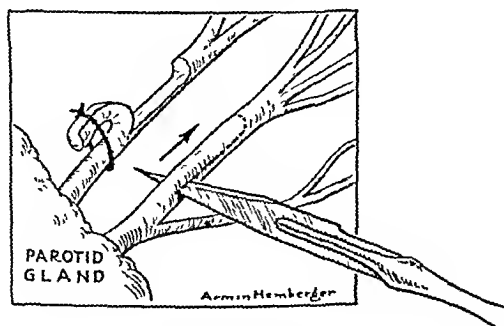


Fig. 2.—Diagrammatic sketch of operation. Note loose ligature holding nerve flap in reverse direction.

spasm are isolated preparatory to partial section. In the earlier cases the appropriate branches were simply divided through about three-quarters of their diameter. In the more recent cases (Fig. 2) a small nerve flap was made, composed of three-quarters or more of each in-



volved branch, and the free proximal segment held loosely in a reversed direction by a lightly tied suture.

Four patients have been operated upon in this manner. The follow-up is incomplete on one patient because of his death, presumably from



Fig. 3.—Photograph of patient, one month after nerve flap operation on right facial nerve.

coronary thrombosis, at a considerable interval after discharge from the hospital; satisfactory relief without paralysis had been obtained up to that time. The operation was repeated on two occasions, at intervals of a year in one case. Satisfactory relief without paralysis was attained after each of the three operations. The last two patients were operated upon within the past year and it is too soon to judge the duration of relief. With the exception of slight temporary weakness of the face immediately after operation, there was very little evidence of motor impairment (Fig. 3). At times, on spontaneous blinking, there appeared to be a slight lag of the involved lid but this was hardly detectable. It is hoped that the nerve flap type of section used in the last two cases may prolong the period of relief. In any case, it is quite feasible to repeat the operation when the spasm recurs.

#### REFERENCES

1. Coleman, C. C.: Surgical Treatment of Facial Spasm, *Ann. Surg.* 105: 647, 1937.
2. Howe, H. A., Tower, S. S., and Duel, A. B.: Facial Tic in Relation to Injury of the Facial Nerve, *Arch. Neurol. & Psychiat.* 38: 1190, 1937.

## OBSERVATIONS AND SURGICAL ASPECTS OF THE CAROTID SINUS REFLEX IN MAN

BRONSON S. RAY, M.D., AND HAROLD J. STEWART, M.D.,  
NEW YORK, N. Y.

*(From the Departments of Surgery and Medicine of the New York Hospital and Cornell University Medical College)*

THE carotid sinus reflex began to assume importance as a factor in the control of vasomotor and other autonomic effects with the experimental work in animals by Hering (1927<sup>6</sup>), de Castro (1928<sup>2</sup>), and Heymans (1929<sup>7</sup>). To Weiss and his co-workers goes much of the credit for bringing to wide attention the significance of the carotid sinus reflex, particularly in its abnormal phases, in man. In 1933 Weiss and Baker<sup>17</sup> presented evidence to show that the abnormal state of the carotid sinus reflex may be responsible for certain symptoms, the most spectacular of which is syncope. Increasing evidence of the existence of what has come to be known as the "carotid sinus syndrome" has now been reported by numerous observers.<sup>4, 5, 10, 11, 13, 18</sup> It has developed that the carotid sinus is but one of many components on the afferent side in the reflex maintenance of the tonus of the autonomic nervous system. Because of this fact there has been misgiving on the part of some in accepting unqualifiedly the carotid sinus syndrome as a manifestation of hypersensitivity of the carotid sinus alone. Our experiences with the carotid sinus reflex in a selected group of surgical cases may serve to add to the accumulating information in this field of inquiry.

A brief review of the significant aspects of the carotid sinus reflex will serve to summarize the subject. Elsewhere the details may be found in monographs.<sup>5, 17</sup>

The carotid sinus may be thought of as comprising the bulbous dilatation of the first portion of the internal carotid artery and perhaps small contiguous portions of the external and common carotids. Its walls are supplied by a dense plexus of nerves lying in the "Y" of the bifurcation of the common carotid (Fig. 1). This plexus connects by way of the "carotid sinus nerve" (nerve of Hering) with the ninth cranial (glossopharyngeal) nerve and also with the tenth (vagus) and twelfth (hypoglossal) cranial nerves and the cervical sympathetics.<sup>15</sup> Certain of the receptor endings appear to respond to stretch or pressure and others to chemical stimuli.<sup>8</sup> Impulses which arise in the carotid sinus pass centrally to stimulate numerous autonomic centers. Constant stimuli from the carotid sinus exert a tonic inhibitory effect on the

Presented at the meeting of the Society of University Surgeons, Cincinnati, Ohio, Feb. 12-14, 1942.

vasomotor centers and when the afferent impulses subside these centers overreact, at least until compensated for by the numerous other afferent mechanisms. Thus, changing arterial pressure within the carotid sinus brings about a fall in systemic blood pressure and slowing of cardiac rate with increase of the intrasinal pressure, and the reverse with a decrease in intrasinal pressure.

When abnormal sensitivity of the carotid sinus reflex exists in man the evidence indicates that there is an increase in the afferent impulses. This results in a variety of symptoms of overactivity of the autonomic system depending upon which of the efferent pathways are implicated. In persons more severely afflicted syncope may be one of the symptoms.

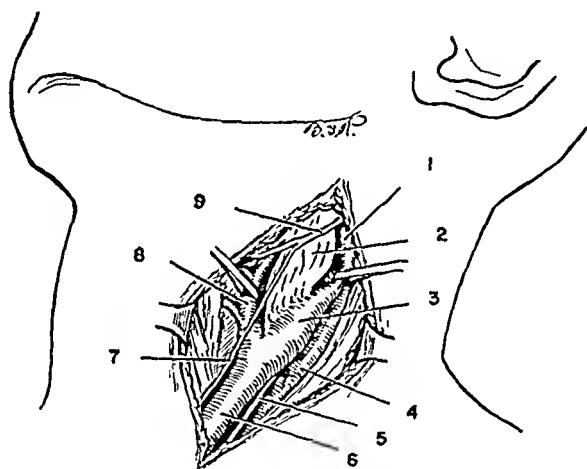


Fig. 1.—Dissection of the carotid sinus. 1, Internal carotid artery; 2, nerve fibers to carotid sinus; 3, carotid sinus; 4, internal jugular vein; 5, vagus nerve; 6, common carotid artery; 7, descending hypoglossal nerve; 8, external carotid artery; 9, hypoglossal nerve.

The syncopal attacks may occur without warning or be preceded by such symptoms as dizziness (rarely vertigo), paresthesias in the extremities, blurring of vision, weakness, confusion, sleepiness, and epigastric distress. The syncope is usually associated with hyperpnea, successive pallor and flushing of the face, perspiration, falling, convulsive movements, varying degrees of decline in blood pressure, slowing of the cardiac rate, and irregularity of cardiac rhythm. The attacks may last a few seconds to several minutes and recovery is usually prompt. The precipitating factors cannot always be discovered but often the attacks result from sudden turning of the head or pressure on the neck. The attacks most often occur while persons are in the erect or sitting position and rarely while in the recumbent position. The frequency and severity of the attacks vary greatly even in the same individual. The syndrome is more common in middle-aged and elderly persons, and among those

afflicted is a high incidence of associated disorders, the most common of which are emotional instability, peptic ulcer, vascular hypertension, arteriosclerosis, angina pectoris, syphilis, cervical lymphadenopathy, and digitalis intoxication. The diagnosis is made from the history and from the reproduction of the attack by pressure over the abnormal carotid sinus.

The syncope which results from stimulation of the carotid sinus nerves occurs through one of three mechanisms.<sup>5, 17</sup> Thus, the syndrome can be divided into types on the basis of changes in the cardiac rate and the blood pressure and on the effect of certain drugs on these manifestations during stimulation of the carotid sinus: (1) the "vagal type" in which syncope results from cerebral anoxia due to reflex cardiac asystole, (2) the "depressor type" in which syncope results from cerebral anoxia due to fall in systemic blood pressure, and (3) the "cerebral type" in which syncope ensues without any significant change in cardiac rate or in blood pressure or possibly without change even in cerebral blood flow.

#### EXPERIENCES WITH THE CAROTID SINUS REFLEX IN SURGICAL CASES

A review of experiences with a few selected cases subjected to operation will serve best to illustrate various normal and abnormal activities of the carotid sinus reflex and also to indicate the significance of this reflex in the field of surgery.

##### *A. Four Cases of Hypersensitive Carotid Sinus Reflex (Vagal Type) in Which the Sinus Was Denervated.*

CASE 1.—O. R., a 58-year-old retired locomotive engineer, complained of recurring attacks of syncope for seven years.

He had been found by serologic tests to have syphilis and had received intensive treatment for four years. He had a cerebral vascular accident at the age of 55 which left a faint residual left-sided weakness. He had a few attacks characterized by dyspnea and mild precordial pain, thought to be angina pectoris, for one year.

The first attack of syncope had occurred seven years before. While leaning out the cab window of a locomotive he suddenly lost consciousness and fell. Since then similar attacks had occurred, first on an average of once a month, more recently as often as several times a day. He related his syncope to no constant factor unless it be to sudden turning of the head in one or another direction. The attacks often occurred without warning but sometimes were preceded by blurring of vision and a sensation as though his heart had stopped. If standing, he was likely to fall; if seated, he remained seated; no attacks occurred in recumbency. His unconsciousness lasted for an estimated time of six to twenty seconds and on return of consciousness he noted forceful heart action, profuse sweating, and a sense of weakness which often lasted for thirty minutes.

The physical examination revealed generalized arteriosclerosis of moderate degree. The carotid arteries were enlarged, more especially on the right. The heart was slightly enlarged to the left but otherwise was normal. Blood pressure averaged 156/70 and the cardiac rate 80.

The electrocardiogram showed normal rhythm and left axis deviation, probably indicative of moderate hypertrophy of the left ventricle. Otherwise the form of the tracing was essentially normal.

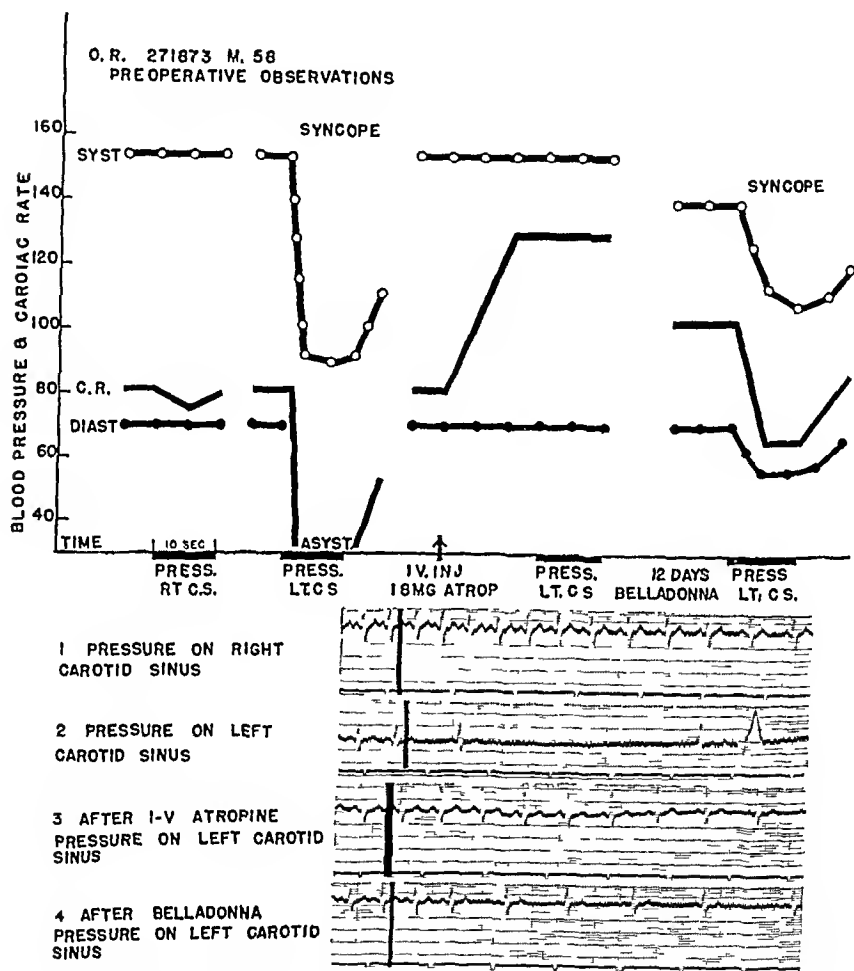


Chart 1 (Case 1) —Graphic representation of the changes observed in the pre-operative tests as listed in the text. The simultaneous electrocardiographic records demonstrate the effects of the various tests on cardiac rate and rhythm. The solid black line from the top to the bottom of the electrocardiographic tracing indicates the application of pressure to the carotid sinus. The time intervals are 0.04 of a second, the Jacquet marker indicates seconds.

Special tests showed (Chart 1): (a) pressure over the right carotid sinus, no essential change in blood pressure, cardiac rate, or state of consciousness; (b) pressure over the left carotid sinus, marked drop in blood pressure, asystole for four seconds with resumption of slow abnormal contractions before release of the pressure and complete syncope; (c) after intravenous injection of atropine, all effects of pressure on the sinus were abolished, (d) after twelve days of belladonna in sufficient amounts to cause blurred vision, dry mouth, and pulse rate of 102; pressure on the left carotid sinus caused less change in blood pressure and cardiac rate than formerly but the same degree of syncope.

At operation ether anesthesia was employed and the left carotid arteries at the bifurcation were exposed (Fig. 1). The arteries were sclerotic, containing visible atheromatous plaques in their walls, and the internal carotid was moderately enlarged. Even with general anesthesia the carotid sinus reflex was intact and tests showed (Chart 2): (a) Pressure on the carotid sinus caused fall in blood pressure and cardiac asystole; (b) occlusion of the common carotid on two different trials diminished the intrasinal pressure and caused the reverse effects; (c) the injection of procaine into the carotid sinus nerves caused considerable rise in blood pressure and cardiac rate and abolished the reflex. The carotid sinus nerves and carotid body were excised and the blood pressure and pulse gradually returned to normal in thirty minutes.

During one year's follow-up there was no return of spontaneous attacks of syncope and no changes could be induced by pressure on the carotid sinuses

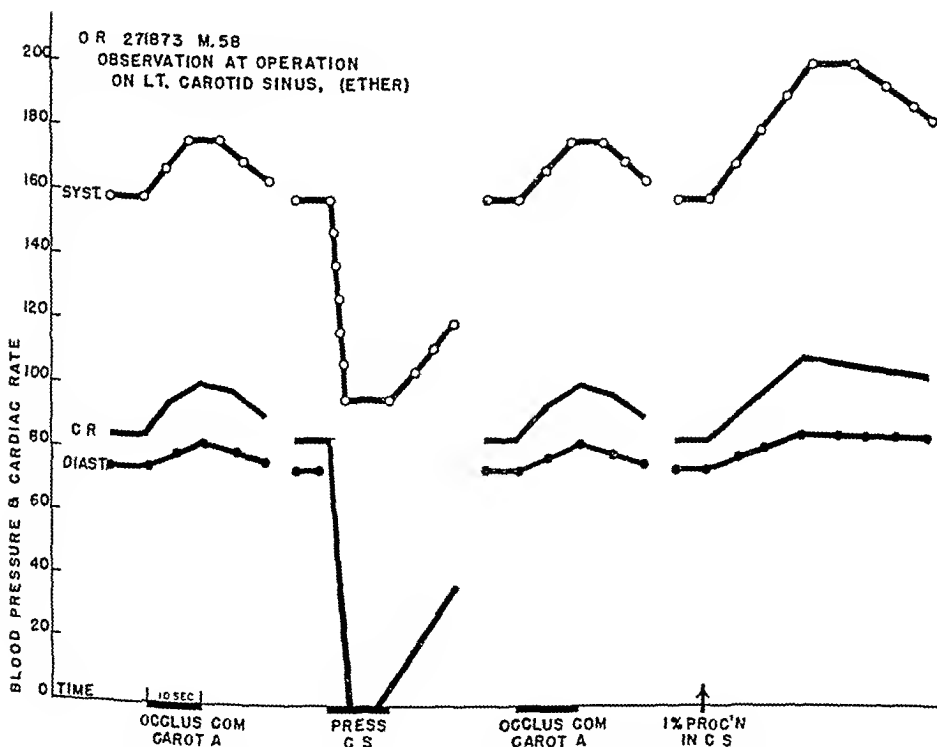


Chart 2 (Case 1)—Graphic representation of the changes observed in tests at operation on the left carotid sinus as listed in the text.

The hypersensitive carotid sinus reflex was limited to the side on which the carotid sinus demonstrated the greater enlargement. The reflex was of the "vagal type" since the response was abolished by a suitable amount of atropine given intravenously, but the failure of atropine to prevent syncope when given in smaller doses by mouth is significant. It indicates that in the more severe cases, at least, atropine is of no value therapeutically and it has the disadvantage of producing tachycardia and a group of unpleasant symptoms.

In the observations at operation it is important to note that ether anesthesia did not affect the reflex response induced by pressure on the carotid sinus.

The increase in blood pressure and cardiac rate following reduction in intrasinal pressure induced by occlusion of the common carotid was of the same degree on repeated trials. But a reduction in intrasinal pressure of sufficient degree to produce changes equal to those resulting from interruption of the carotid sinus nerves would probably require occlusion not only of the common carotid but of the external and the distal internal carotids as well.

CASE 2—J. P., a 68 year old retired business-man, complained of recurring faintness for two years. He had a long history of peptic ulcer and had had a gastrojejunostomy ten years before, without complete relief of symptoms.

For two years he had recurring pain in the right side of the neck radiating to the angle of the jaw and ear, occasionally to the eye and forehead. For the same period he had beneath the angle of the right jaw a swelling which at times seemed more prominent and slightly tender. When these symptoms were most noticeable he was likely to have frequent attacks of sudden faintness. Even though he never lost consciousness he was momentarily confused and the attacks had grown so frequent that his activities were limited. He believed that smoking made him more susceptible to attacks.

The physical examination revealed general arteriosclerosis. The bulbous portions of the internal carotid arteries were prominent and almost aneurysmal; the right was more prominent than the left and tender to palpation. The cardiac findings were normal. The blood pressure averaged 116/74 and the cardiac rate 68.

The electrocardiogram showed moderate left axis deviation, but on the whole the form of the tracing was normal.

Special tests showed (Chart 3). (a) pressure over the left carotid sinus, slight change in blood pressure and cardiac rate, (b) pressure over the right carotid sinus, marked drop in blood pressure, asystole for six seconds with resumption of slow rate before release of pressure, and complete syncope preceded by numbness in the left lower extremity, (c) after intravenous injection of atropine all effects of pressure on either carotid sinus were abolished.

At operation a limited amount of procaine was employed locally and the right carotid arteries at the bifurcation were exposed. The vessels were slightly sclerotic and the bulbous portion of the internal carotid was twice normal size. On manipulation of the arteries pain similar to that complained of prior to operation occurred in the neck, jaw, and behind the ear. Stimulation of the walls of the carotid arteries with a faradic current produced a localized pain which did not radiate. This stimulation caused no change in blood pressure, cardiac rate, or state of consciousness. Other tests showed (Chart 4). (a) Pressure on the carotid sinus caused fall in blood pressure, cardiac asystole, and syncope, (b) occlusion of the common carotid caused rise in blood pressure and cardiac rate, while sudden release of the occlusion, by virtue of sudden increase in intrasinal pressure, caused temporary fall in pressure and cardiac rate below the normal; (c) procaine injected into the carotid sinus nerves caused moderate rise in blood pressure and cardiac rate and abolished the reflex. The carotid sinus nerves and carotid body were excised and the blood pressure and cardiac rate gradually returned to normal after six hours.

During eight months' follow-up there were no spontaneous attacks of syncope and no changes could be induced by pressure on the right carotid sinus. Pressure on the left carotid sinus produced the same moderate changes as occurred originally.

Carotodynia appeared to accompany the hypersensitive carotid sinus reflex and probably both were the result of local pathology in the carotids. Manipulation and faradic stimulation of the walls of the carotids readily demonstrated their pain sensitivity.

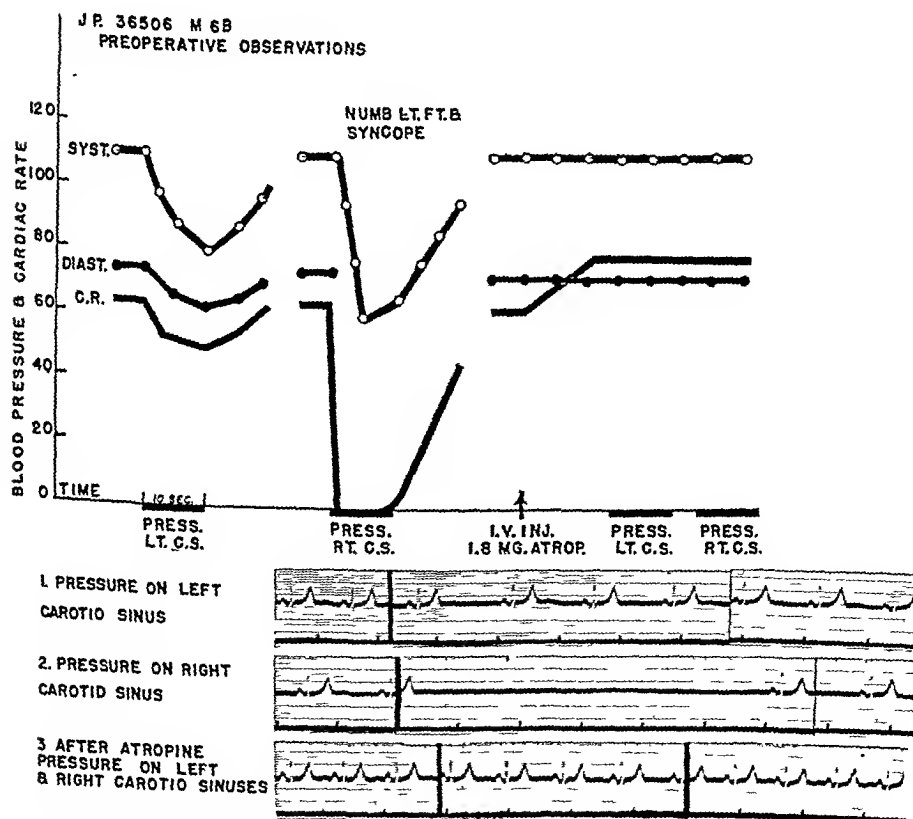


Chart 3 (Case 2) —Graphic representation of the changes observed in the preoperative tests, as listed in the text. The simultaneous electrocardiographic records demonstrate effects of the various tests on cardiac rate and rhythm

In the other observations at operation it is significant that the increase in blood pressure and cardiac rate following sudden occlusion of the common carotid was of greater degree than that which occurred after injection of procaine into the carotid sinus nerves. This is in keeping with the frequent observation that in the carotid sinus reflex the degree of the response is in direct proportion to the suddenness and the amount of pressure on the carotid sinus. The lesser response with an-



esthetization of the sinns nerves may be accounted for by the slower interruption of the afferent stimuli, thus affording time for compensatory reactions.

CASE 3.—P. E., a 58-year-old stationary engineer, complained of recurring syncope for six months. He had a seven years' history of mild symptoms of peptic ulcer made worse by alcohol and overindulgence in tobacco. A lesion presumed to be a chancre had been treated locally by cautery in 1910; the serologic tests for syphilis were normal subsequently.

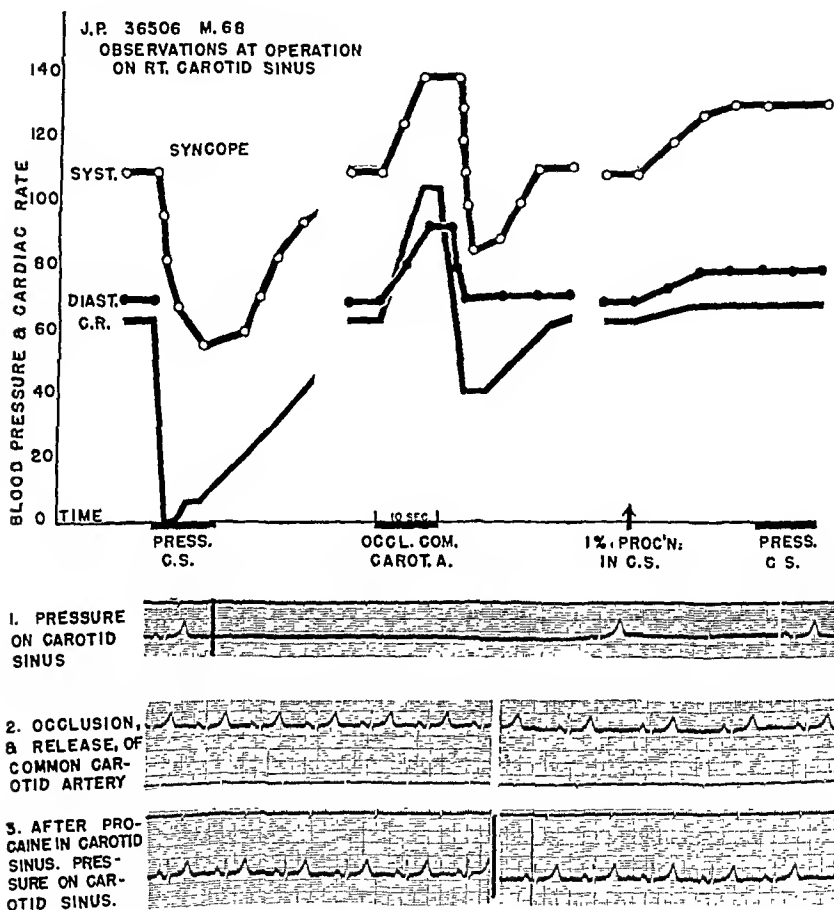


Chart 4 (Case 2).—Graphic representation of the changes observed in tests at operation on the right carotid sinus, as listed in the text. The simultaneous electrocardiographic records demonstrate effects on cardiac rate and rhythm of the various tests.

For six months he had a succession of attacks of sudden faintness when leaning over to tie his shoes, leaning over the wash bowl, and on turning his head to the left. The attacks occurred on several different occasions when on entering his house he turned to hang his hat on a hook to his left. Although the attacks never progressed to total loss of consciousness or falling, they were distressing and made him fearful at his work about machinery.

The physical examination revealed generalized arteriosclerosis of moderate degree. The common carotid arteries were prominent and the bulbous portions of the internal carotids were enlarged. The cardiac findings were normal. The blood pressure averaged 120/70 and the cardiac rate 65.

The electrocardiogram showed normal rhythm and slight left axis deviation, probably associated with beginning hypertrophy of the left ventricle. But the form of the tracing was essentially normal.

Special tests showed (Chart 5): (a) pressure over the right carotid sinus, slight drop in blood pressure and slowing of cardiac rate; (b) pressure over left carotid

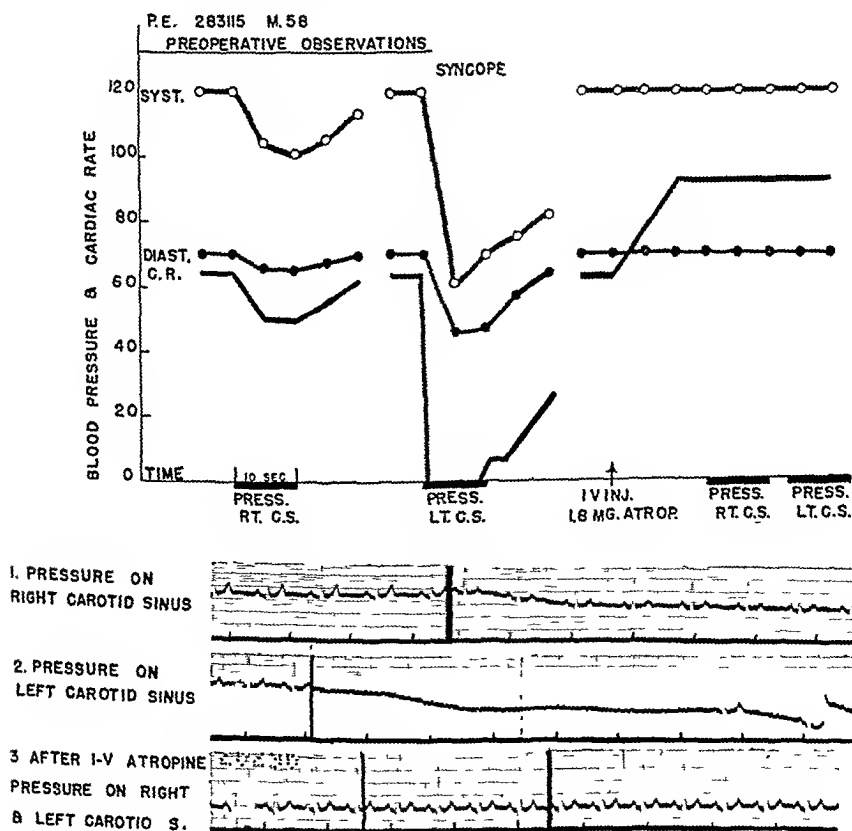


Chart 5 (Case 3).—Graphic representation of the changes observed in the preoperative tests as listed in the text. The simultaneous electrocardiographic records demonstrate the effects of the various tests on cardiac rate and rhythm.

sinus, marked drop in blood pressure, cardiac asystole for six and one half seconds with resumption of slow rate before release of pressure, and complete syncope; (c) after intravenous injection of atropine all effects of pressure on either carotid sinus were abolished.

At operation a limited amount of procaine was employed locally and the left carotid arteries at the bifurcation were exposed. The vessels were markedly sclerotic and almost rigid and the internal carotid was enlarged. Tests showed (Chart 6): (a) Occlusion of the internal carotid 4 cm. above the bifurcation caused moderate fall in blood pressure and slowing of cardiac rate; (b) occlusion of the common carotid produced no change; (c) pressure on the carotid sinus caused marked drop

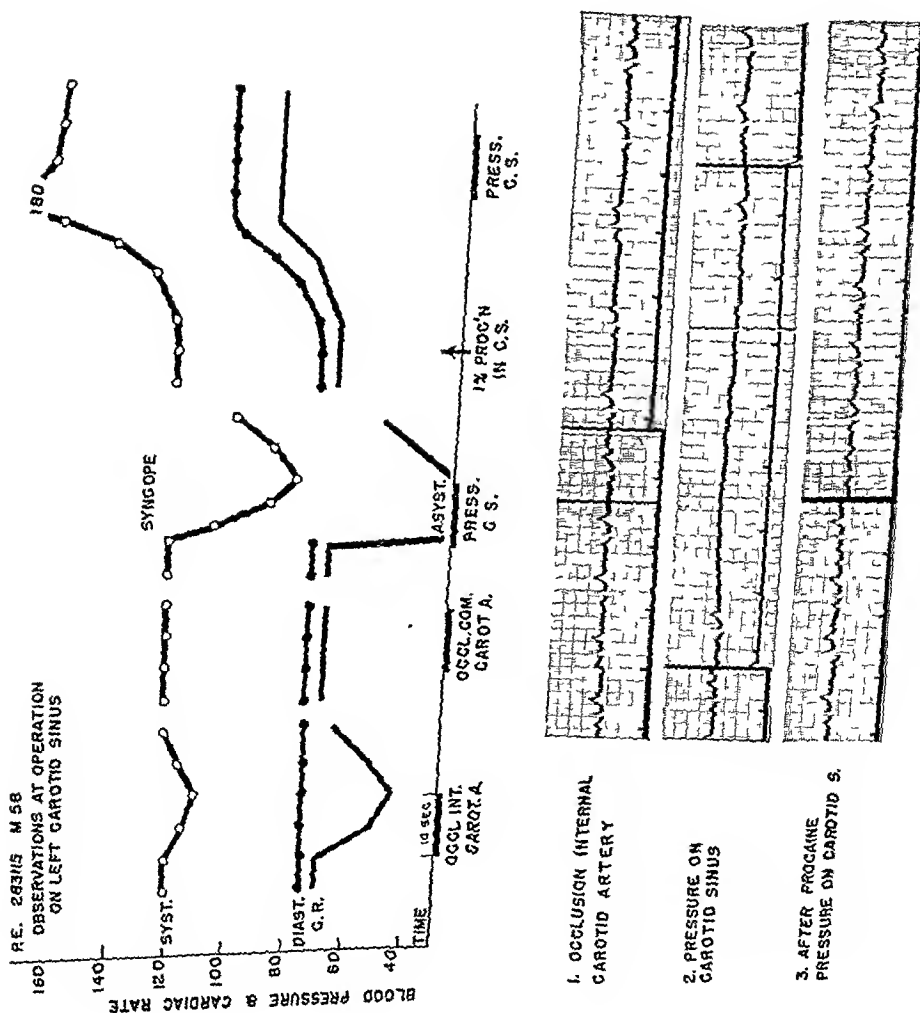


Chart 6 (Case 3).—Graphic representation of the changes observed in tests at operation on the left carotid sinus, as listed in the text. The simultaneous electrocardiographic records demonstrate effects of the various tests on cardiac rate and rhythm.

in blood pressure, cardiac asystole and syncope; (d) injection of procaine into the carotid sinus nerves caused marked rise in blood pressure and moderate rise in cardiac rate and abolished the reflex. The carotid sinus nerves and carotid body were excised and the blood pressure and cardiac rate gradually returned to normal in one half hour.

During ten months' follow up there were no spontaneous attacks of syncope and no changes could be induced by pressure on the denervated carotid sinus. Pressure on the opposite sinus produced the same moderate changes as occurred originally.

At least two of the observations at operation are of interest. One, occlusion of the internal carotid 4 cm above the bifurcation, stimulated the sinus reflex. Whether the stimulation occurred by direct pressure on nerve endings that extend above the bulbous portion of the internal carotid or by increasing the intrasinal pressure cannot be determined. But it was demonstrated by pressure tests in this and at least one other case that the carotid sinus nerve endings do not extend down into the wall of the common carotid any appreciable distance.

The other observation of interest is the absence of effect on lowering the intrasinal pressure by occlusion of the common carotid, yet a marked effect on anesthetization of the carotid sinus nerves. The most tenable explanation is that in the presence of a very sclerotic and rigid arterial wall the effects of lowering the intrasinal pressure are nullified by the failure of the sinus to collapse.

CASE 4—H. L., a 59 year old retired fireman, complained that when anything pressed, even gently, on the right side of his neck he fainted.

He had had a carcinoma of the lower lip on the right side excised surgically on two occasions in the previous six years. There was a question of metastasis to the cervical nodes and he had been concerned about palpable nodes in his neck, especially on the right side.

For about eight months he had found that palpation of the right side of his neck just beneath the jaw by physicians or by himself almost always resulted in an attack of faintness with either partial or complete loss of consciousness. Pressure here from shaving or from a collar also induced the attacks but as long as no pressure occurred there were no attacks.

The physical examination revealed the scar of an apparently cured lesion of the lower lip on the right. There was considerable oral infection due to decayed teeth and a number of nontender cervical nodes on both sides of the neck but most pronounced on the right. The carotid arteries on both sides of the neck were prominent. There was a moderate degree of generalized arteriosclerosis. The cardiac findings were normal but for slight enlargement of the heart to the left. The blood pressure was 164/90 and the cardiac rate 80.

The electrocardiogram showed normal sinus rhythm and moderate left axis deviation. The form of the tracing was essentially normal.

Special tests showed (Chart 7): (a) pressure over the left carotid sinus, a decided fall in blood pressure and cardiac rate, and slight syncope, (b) pressure on the right carotid sinus, marked drop in blood pressure, cardiac asystole with a few abnormal contractions occurring during the period of pressure, and simultaneous loss of consciousness with convulsive movements of the extremities more marked on the



In this case the carotid sinus reflex was hypersensitive on both sides but much more accentuated on the right. In the preoperative tests it is interesting that with stimulation of the sinus reflex on the right there occurred convulsive movements only on the left. This would suggest that changes occurred in the right cerebrum to cause the convulsions, yet when the effects of the reflex on the systemic blood pressure and

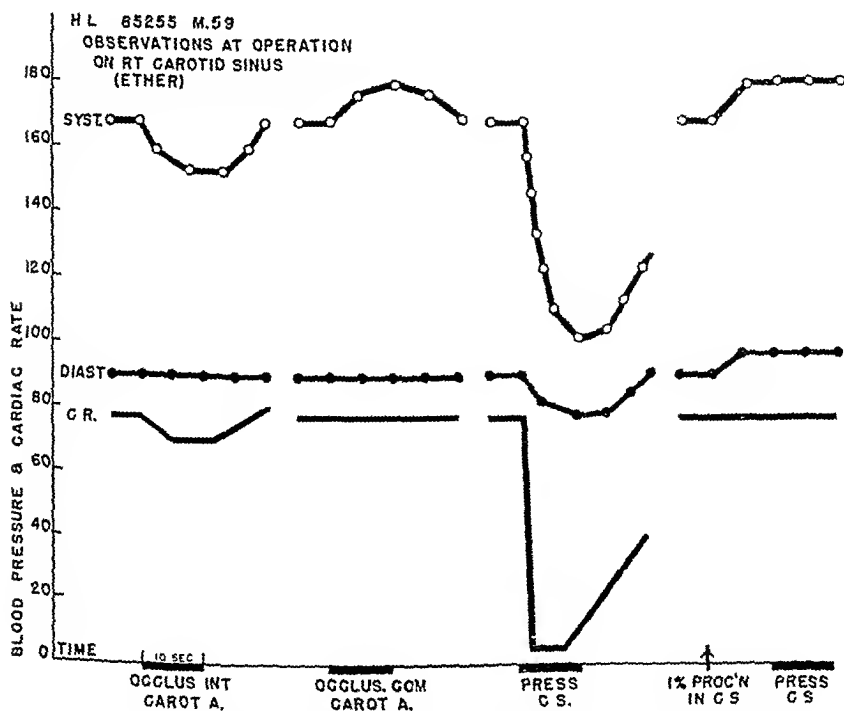


Chart 8 (Case 4) —Graphic representation of the changes observed at operation on the right carotid sinus, as listed in the text

the cardiac rate were abolished by intravenous atropine the convulsions, as well as the syncope, failed to develop also. Since the effect of atropine is assumed to be peripheral, and the origin of the convulsions was central, the abolition of the convulsions by injection of atropine is a paradox which is not readily explained.

The rise in blood pressure was slight and change in cardiac rate nil after anesthetization of the carotid sinus nerves which suggests that in people with hypertension interruption of the afferent part of one carotid sinus reflex may be accompanied by little change in blood pressure.

*B. Case of Hypersensitive Carotid Sinus Reflex (Cerebral Type) Associated With Tuberculous Nodes in the Neck in Which Cure Followed Excision of the Nodes.*

CASE 5.—S. D'A., a 40-year-old plumber, complained of recurring swelling in the neck and of fainting attacks.

He had had recurring tuberculous nodes in the neck for about ten years, treated with numerous local excisions. For the past six months several fairly large painless swellings had existed beneath the angle of the right jaw. For three months he had daily attacks of syncope heralded by a full feeling in the head, dizziness, and general weakness. He never lost consciousness and never fell but was confused for eight to ten seconds and following this broke out in perspiration, especially about the face, and felt nauseated. The attacks usually occurred while he was standing but occasionally while sitting.

Physical examination revealed a well-nourished healthy looking man. There were several palpable nontender nodes in both sides of the neck, the largest being

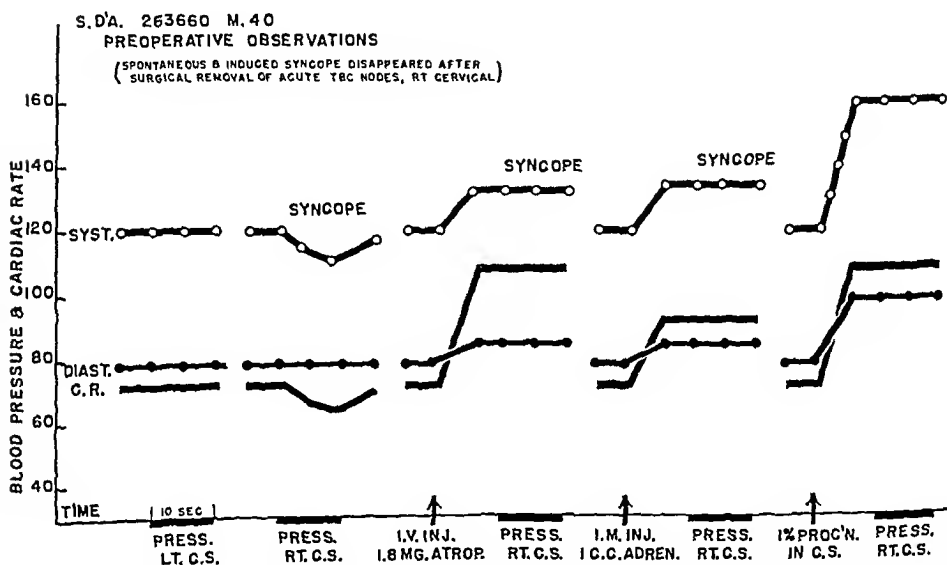


Chart 9 (Case 5).—Graphic representation of the changes observed in the pre-operative tests as listed in the text.

about 2½ cm. in diameter and lying just over the right carotid sinus. There was no active pulmonary tuberculosis. The cardiac findings were normal. The blood pressure was 120/80 and the cardiac rate 70.

Special tests showed (Chart 9): (a) pressure over the left carotid sinus, no effects; (b) pressure on the node over the right carotid sinus, only slight fall in systolic pressure and cardiac rate but complete syncope; (c) intravenous injection of atropine abolished the effects on blood pressure and cardiac rate but not the syncope following pressure on the right carotid sinus; (d) intramuscular injection of adrenalin had essentially the same effects as injection of atropine; (e) injection of procaine into the right carotid sinus caused a rise in blood pressure and cardiac rate and syncope did not occur with pressure over the sinus.

At operation the larger cervical nodes on the right side were excised locally and no observations were made on the carotid sinus reflex at the operation.

During one year after operation there were no spontaneous attacks of syncope and none could be induced by pressure on the carotid sinuses.

The "cerebral type" of syncope occurring with a hypersensitive carotid sinus reflex is the most interesting of the three types of syncope. Its mechanism is not at all clear since there are no demonstrable changes in blood pressure or cardiac rate and some deny the existence of this type of syncope. If it does exist unqualifiedly it is the only example in which loss of consciousness alone occurs from the stimulation of afferent nerves. In the study of this patient every effort was made to avoid suggestion or making him aware of anticipated phenomena.

*C. Two Cases Illustrating Reactions of the Normal Carotid Sinus Reflex When Examined at Operation.*

CASE 6.—M. L., a 16 year old girl, had a verified congenital arteriovenous anomaly existing principally in the pial vessels over the left parietal cerebral hemisphere. The lesion caused local convulsive seizures in the right extremities without loss of consciousness.

Physical examination revealed a cephalic bruit on the left and slight impairment of sensation on the right side of the body. In other respects she appeared to be normal. The blood pressure was 110/60 and the cardiac rate 80. The form of the electrocardiogram was normal.

The carotid arteries in the neck were not remarkable on palpation. Pressure over each carotid sinus caused slight fall in systolic pressure and slight slowing of cardiac rate. Pressure on the left carotids caused diminution in the cephalic bruit and this was the indication for carotid ligation.

At operation procaine was employed locally and the left carotid arteries at the bifurcation were exposed. The arteries were slightly larger than average but otherwise appeared normal. Tests showed that (Chart 10): (a) Occlusion of the common carotid caused slight rise in systolic pressure and cardiac rate and on sudden release of the occlusion there was prompt return to normal but no drop in blood pressure or slowing of cardiac rate below the original level, (b) pressure on the carotid sinus caused slight fall in systolic pressure and slowing of cardiac rate; (c) gradual injection of procaine into the carotid sinus nerves (followed by ligation of the common carotid artery) caused moderate rise in blood pressure and in cardiac rate with return to normal in ten minutes. There were no untoward effects from ligation of the carotid.

CASE 7.—M. B., a 19 year old boy, had a verified congenital arteriovenous anomaly existing largely in the pial vessels over the right parietal cerebral hemisphere. This lesion caused local convulsive seizures in the left extremities without loss of consciousness.

Physical examination revealed a cephalic bruit of low intensity and slight changes in the reflexes on the left side of the body. In other respects he appeared to be a normal healthy boy. The cardiac findings were normal. The blood pressure was 115/75 and the cardiac rate 64. The form of the electrocardiogram was essentially normal.

The carotid arteries in the neck were not remarkable and repeated pressure over the carotid sinuses failed to produce any change in blood pressure, the cardiac rate, or the state of consciousness. Occlusion of the right carotids did, however, diminish the cephalic bruit and this was the indication for carotid ligation.



At operation procaine was employed locally and the right carotid arteries at the bifurcation were exposed. The vessels and adjacent structures were of normal appearance. Tests showed that (Chart 11): (a) Occlusion of the common carotid caused prompt and marked rise in blood pressure and cardiac rate with return to

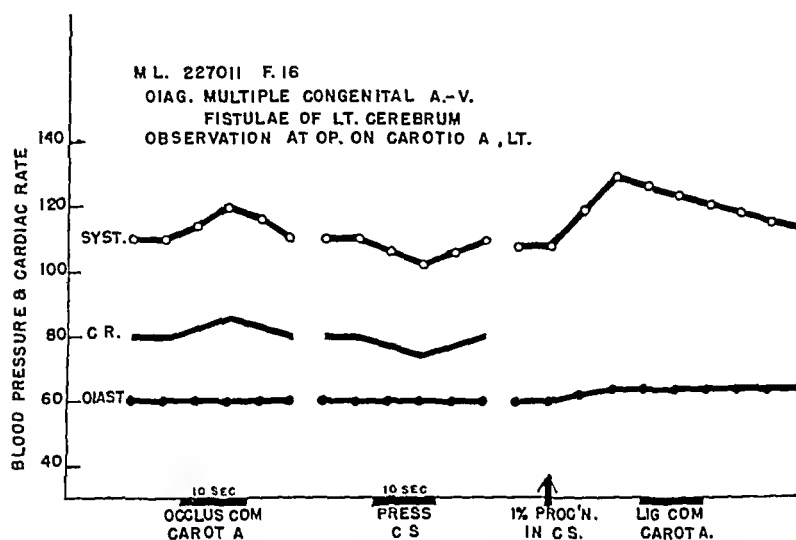


Chart 10 (Case 6) —Graphic representation of the changes observed at operation on direct stimulation of a normal carotid sinus, as listed in the text

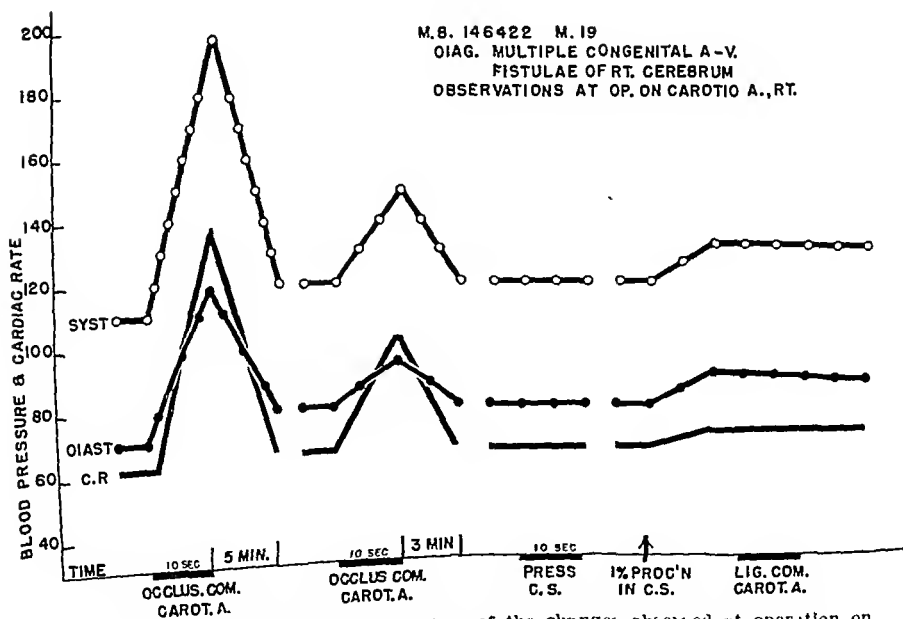


Chart 11 (Case 7). —Graphic representation of the changes observed at operation on direct stimulation of a normal carotid sinus, as listed in the text

normal five minutes after release of the occlusion; (b) repetition of the occlusion of the common carotid caused the same type of response as before but of less degree; (c) pressure on the carotid sinus caused no changes; (d) injection of procaine into the carotid sinus nerves (followed by ligation of the common carotid) caused only a moderate rise in blood pressure and cardiac rate with return to normal in fifteen minutes. There were no untoward effects from the ligation of the carotid.

While many tests have been made on the effects of pressure on the normal carotid sinus there is limited opportunity to employ direct tests on the normal sinuses that has been exposed at operation. In Cases 6 and 7 there are lesions of the cerebral vasculature but it is reasonable to assume that the carotid sinus reflex in each is normal. The responses of the normal carotid sinus are thought to be variable within limits and the responses in these two cases are confirmatory.

The responses in Case 6 probably represent those existing in the majority of people with a normal carotid sinus reflex. In Case 7 the absence of hypersensitivity of the sinus reflex is demonstrated by the lack of response on direct pressure on the sinus. The marked rise in blood pressure and cardiac rate on sudden reduction of intrasinus pressure by occlusion of the common carotid can be considered normal though not constant in all cases. The fact that a repetition of the test shortly after gave a response of less degree, and that after a few minutes interruption of the reflex by anesthetization of the carotid sinus nerves gave little response at all, indicates the sustained effects of compensatory mechanisms once they are induced.

#### *D. Case Illustrating Syncope Due Not to Hypersensitive Carotid Sinus Reflex But to Arterial Occlusion Alone*

CASE 8.—C. E., a 61 year old woman, struck her head in a fall resulting in an arteriovenous fistula between the intracranial portion of the internal carotid artery and the cavernous sinus on the right. She suffered from headache and loss of motion in the right eye.

Physical examination revealed complete ophthalmoplegia, impaired vision, and periorbital edema on the right. There was a loud cranial bruit and general arterio-sclerosis of moderate degree. The heart was normal, the blood pressure 110/70, and the cardiac rate 68.

Ligation of the carotids in the right side of the neck was planned as a therapeutic measure. However, trial occlusion of the right carotids always resulted in prompt loss of consciousness and convulsive movements on the left side of the body. Since the patient's neck was short and thick it was never possible to determine definitely whether any pressure sufficient to occlude the common carotid alone might not at the same time be stimulating the carotid sinus reflex as well.

Special tests showed that (Chart 12) (a) Pressure on the left carotid sinus caused no changes; (b) pressure on the right carotid sinus caused syncope and left convulsive movements but no change in blood pressure or cardiac rate; (c) after intravenous injection of atropine, pressure on the right carotid sinus caused the same

response as before; (d) after injection of procaine into the right carotid sinus nerves syncope still followed pressure over the right carotid sinus.

The observations demonstrated the responsibility for syncope following pressure on the carotids to rest wholly in the cerebral anoxia due to carotid occlusion. Thus, therapeutic ligation of the carotids was shown to be unsafe.

This case illustrates the usefulness of employing tests to demonstrate the presence or absence of a hypersensitive carotid sinus reflex. Doubtless therapeutic carotid ligation has been denied patients in the past because syncope occurred with trial occlusion of the carotids by pressure on the neck when exclusion of the carotid sinus reflex would have indicated the safety of the ligation.

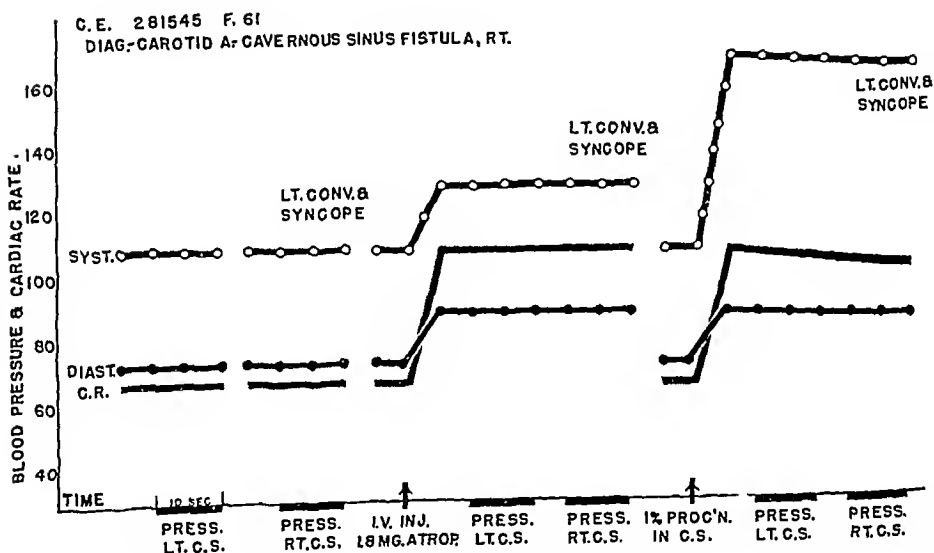


Chart 12 (Case 8).—Graphic representation of the changes observed in the tests, as listed in the text.

### *E. Five Cases Illustrating the Variable Role of the Glossopharyngeal Nerve in the Transmission of the Afferent Impulses From the Carotid Sinus.*

CASE 9.—M. K., a 63-year-old man, had intractable pain from carcinoma and osteomyelitis of the right mandible. There was little generalized arteriosclerosis. The heart was normal. Blood pressure was 130/80 and the cardiac rate 80. Section of the fifth and ninth cranial nerves was advised for relief of pain.

At operation ether anesthesia was employed and the right glossopharyngeal nerve was cut intracranially. In the ten minutes following, the blood pressure rose steadily from 130/80 to a level of 160/95, then gradually returned to normal in the next fifteen minutes. In the same period the pulse rate rose and fell ten points. The postoperative blood pressure and pulse rate were the same as the preoperative.

CASE 10.—C. Y., a 61-year-old man, had intractable pain from carcinoma involving the right maxilla, mandible, and pharynx. There was a moderate degree of generalized arteriosclerosis. The heart was normal. The blood pressure was 130/80 and the cardiac rate 80. Section of the fifth, ninth, and tenth cranial nerves and upper cervical sensory roots was advised for relief of pain.

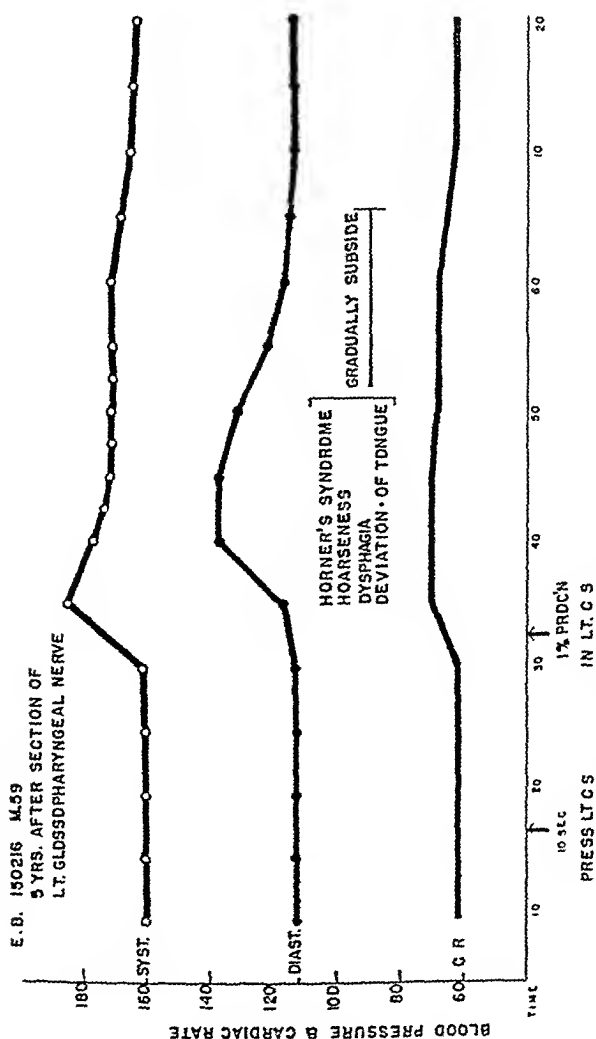


Chart 13 (Case 11).—Graphic representation of the changes observed on anesthetization of the left carotid sinus after section of the left glossopharyngeal nerve

At operation procaine was employed locally and the right glosso-pharyngeal nerve was cut intracranially. In the ten minutes following, the blood pressure rose from 120/75 to 120/75, then gradually returned to the original level in the next fifteen minutes. In the same period the pulse rate rose and fell eight points. When the vagus nerve was cut intracranially later there was an accompanying rise in pulse rate of twenty points, but no change in blood pressure. The post-operative blood pressure and pulse rate were the same as the preoperative.

CASE 11.—E. B., a 59 year-old man, had paroxysmal pain characteristic of glossopharyngeal neuralgia on the left. His general physical condition was good. The heart was normal. Blood pressure was 138/70 and cardiac rate 78.

At operation avertin and ether were employed and the left glossopharyngeal nerve was cut intracranially. In the next six minutes the blood pressure rose from 110/70 to a level of 135/75, then gradually returned to its original level in the next twenty minutes. In the same period the pulse rose twelve points. The postoperative blood pressure and pulse rate were the same as the preoperative.

Five years after section of the left glossopharyngeal nerve, pressure over the right carotid sinus caused marked slowing of the cardiac rate and drop in blood pressure but no syncope, while pressure on the left sinus caused no effects. Anesthetization of the left carotid sinus with 15 c.c. of 1 per cent procaine (Chart 13) caused prompt rise in systolic pressure of twenty five points and in diastolic pressure of twelve points. The cardiac rate increased but six points. There was a gradual return of blood pressure to normal in forty-five minutes, during which the effects of the procaine subsided. This response indicated an intact carotid sinus reflex. Accompanying symptoms of anesthetizing the area were a left Horner's syndrome, hoarseness, and deviation of the tongue to the left.

CASE 12.—G. H., a 58 year old man, had paroxysmal pain characteristic of glossopharyngeal neuralgia, on the left. He had generalized arteriosclerosis. The heart was not enlarged but the cardiac rate was irregular. The blood pressure was 110/80 and the cardiac rate 120. The electrocardiogram showed auricular fibrillation and complexes indicating myocardial damage. After digitalization the cardiac rate and rhythm returned to normal.

At operation procaine was employed locally and the left glossopharyngeal nerve was cut intracranially. This was unaccompanied by any significant change in cardiac rate or in blood pressure.

One year after section of the left glossopharyngeal nerve, pressure over either carotid sinus caused no appreciable effects. Anesthetization of the left carotid sinus with 10 c.c. of 1 per cent procaine (Chart 14) caused prompt rise in systolic pressure of fifty points and in diastolic pressure of sixteen points. The cardiac rate increased but five points. There was a gradual return of blood pressure to normal in thirty five minutes, during which the effects of the procaine subsided. This response indicated an intact carotid sinus reflex. Accompanying symptoms of an anesthetization of the area were left Horner's syndrome and hoarseness.

CASE 13.—G. C., a 40 year old woman, had had the fifth and ninth cranial and the first four cervical sensory roots cut intradurally on the left side for neuralgia of unknown origin. In addition, examination showed palsy of the eleventh and twelfth nerves on the left. The operation had been performed elsewhere and the record of pulse rate and blood pressure during operation was not available. The heart was normal. The blood pressure was 130/80 and the pulse rate 70.

Eighteen months after section of the left glossopharyngeal nerve (plus paralysis of the left hypoglossal) pressure over either carotid sinus caused no appreciable effects. Anesthetization of the left carotid sinus with 20 c.c. of 1 per cent procaine caused a left Horner's syndrome, hoarseness, dysphagia, and tachycardia but no change in blood pressure. This indicated the absence of an intact carotid sinus reflex.

Anatomically the connections of the nerves to the carotid sinus have been shown to be with the ninth, tenth, and twelfth cranial nerves and the cervical sympathetics.<sup>15</sup> The principal nerve with which the sinus has been thought to be supplied is the ninth cranial nerve through the

"carotid sinus nerve" (nerve of Hering). On the basis of experimental denervation of the sinus in dogs it has been concluded that the cardiovascular components of the sinus reflex are conducted solely through the carotid sinus nerve.<sup>3</sup> Bucy<sup>1</sup> cited his experiences with four cases in which, with intracranial section of the ninth cranial nerve, there was a

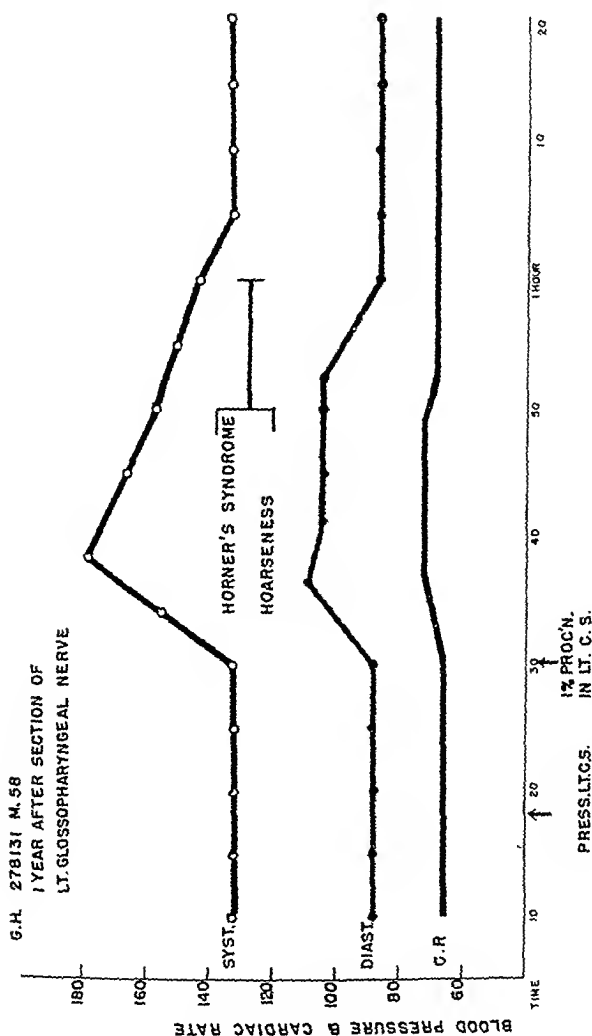


Chart 14 (Case 12).—Graphic representation of the changes observed on anesthetization of the left carotid sinus after section of the left glossopharyngeal nerve.

resultant rise in blood pressure. The conclusion which these and other observations imply is that in man the afferent impulses of the sinus reflex are conducted through the ninth cranial nerve and its branch the carotid sinus nerve.

In four cases (Cases 9 to 12) of intracranial section of the ninth cranial nerve, temporary rise in blood pressure occurred in three but there was no change in the fourth. In two cases (Cases 11 and 12)

subsequent anesthetization of the carotid sinus on the side of operation caused the characteristic rise in blood pressure that occurs with the intact reflex, indicating that the sinus reflex was qualitatively unchanged in these two. In Case 13 anesthetization of the carotid sinus on the side of operation caused no change in blood pressure but in this case there was, in addition to the section of the ninth cranial nerve, a paralysis of the twelfth cranial nerve.

These observations, therefore, indicate that in man the afferent impulses of the carotid sinus reflex are not transmitted solely through the ninth cranial nerve in all instances.

#### COMMENT

When the symptoms of hypersensitive carotid sinus reflex are mild or infrequent, reassurance, instruction in avoiding quick movements of the head or pressure on the neck, and mild sedatives will often suffice to avoid or minimize attacks. X-ray irradiation of the carotid sinus has been suggested as suitable treatment for the hypersensitive reflex<sup>14</sup> but irradiation of tumors in this region sometimes induces a hypersensitive reflex. Prolonged use of atropine, ephedrine, or comparable drugs to control symptoms is not desirable. When symptoms are more severe surgical denervation of the carotid sinus is indicated.

There are no indications that the normal carotid sinus reflex should be of itself the source of serious complications during surgical procedures, but that a hypersensitive reflex possesses potential dangers deserves wider recognition. The anesthetic management,<sup>12</sup> the sensitizing effect of digitalis,<sup>5</sup> and the dangers of operations in the neck in patients with hypersensitivity of the carotid sinus reflex<sup>9, 16</sup> have been emphasized by others. Doubtless there will be increasing evidence of the role of the hypersensitive sinus reflex in the production of surgical complications, many of which have gone unexplained in the past. It might be well for surgeons in their routine preoperative examinations to include pressure on the carotid sinuses of every patient. During operation, in the event of cardiac arrhythmia or asystole, bradycardia, vascular hypotension, and possibly convulsions, infiltration of the area between the external and internal carotid arteries with procaine on the side known to possess a hypersensitive sinus reflex will abolish the reflex and may possibly restore the patient.

#### CONCLUSIONS

1. The diagnosis of hypersensitive carotid sinus reflex is made by the patient's history and a systematic examination of the carotid sinuses.
2. Carotodynia sometimes is associated with the carotid sinus syndrome.

3. The frequency of local abnormalities of the carotid arteries and adjacent tissues on the side of the hypersensitive sinus reflex suggests that the abnormal reflex results from pathology in the sinus.

4. If symptoms of hypersensitive sinus reflex are disagreeable or incapacitating and not controlled by simple measures surgical denervation of the carotid sinns is advisable. The operation causes only transitory alteration of the cardiovascular system.

5. By anesthetizing the carotid sinus nerves it is possible to distinguish between syncope due to a hypersensitive sinus reflex and syncope due simply to cerebral anoxia resulting from carotid occlusion.

6. The glossopharyngeal nerve in man is not in every instance the only nerve through which afferent impulses of the carotid sinus reflex are transmitted.

7. Hypersensitivity of a carotid sinns reflex may play an important role in the production of cardiac arrhythmias, cardiac asystole, and fall in blood pressure occurring during operations, especially operations about the neck.

8. Ether anesthesia cannot be counted upon to abolish a hypersensitive sinus reflex.

9. Infiltration with 1 per cent procaine of the carotid sinus nerves lying in the space between the internal and external carotids always temporarily abolishes the sinus reflex. Simultaneous bilateral anesthetization of the region of the carotid sinus is not advisable because of the possible bilateral laryngeal palsy that might accompany it.

#### REFERENCES

1. Bucy, P.: The Carotid Sinus Nerve in Man, *Arch. Int. Med.* 58: 418-432, 1936.
2. de Castro, F.: Sur la Structure et l'Innervation du Sinus Carotidien de l'Homme et des Mammifères. Nouveaux Faits sur l'Innervation du Glomus Caroticum, *Trav. Lab. Recherch. Madrid* 25: 331, 1928.
3. Code, C. F., Dingle, W. T., and Moorhouse, V. H. K.: The Cardiovascular Carotid Sinus Reflex, *Am. J. Physiol.* 115: 249-260, 1936.
4. Craig, W. McK., and Smith, H. L.: The Surgical Treatment of Hypersensitive Carotid Sinus Reflexes; Report of 13 Cases, *Yale J. Biol. & Med.* 11: 415-422, 1939.
5. Ferris, E. B., Jr., Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, *Medicine* 14: 377-456, 1935.
6. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefäße vom normal-physiologischen, pathologischen und klinischen Standpunkt gleichzeitig über abnormen Kreisla. *Zentralblatt für die klinische Medizin* 1927.
7. Heymans, C.: Le Sinus Carotidien et les Autres Zones Vasosensibles Réflexogènes, London, 1929, H. K. Lewis & Co.
8. Heymans, C., and Rijlant, P.: Le Courant d'Action du Nerf du Sinus Carotidien Intact, *Compt. rend. Soc. de biol.* 113: 69-73, 1933.
9. Leger, L.: Le Danger Sinu-Carotidien des Interventions Cervicales, *Presse méd.* 48: 451-453, 1940.
10. Mulholland, J. H., and Rovenstine, E. A.: Surgery in Carotid Sinus Syndrome, *SURGERY* 9: 751-757, 1941.



11. Robinson, L. J.: Syncope, Convulsions and Unconscious State; Relation to Hyperactive Carotid Sinus Reflex, *Arch. Neurol. & Psychiat.* 41: 290-297, 1939.
12. Roxenstine, E. A., and Cullen, S. C.: The Anesthetic Management of Patients With a Hyperactive Carotid Sinus Reflex, *SURGERY* 6: 167-176, 1939.
13. Smith, H. L.: Fainting Attacks Resulting From Hypersensitive Carotid Sinus Reflexes, *Am. Heart J.* 14: 614-619, 1937.
14. Stevenson, C. A.: Use of Roentgen Therapy in Carotid Sinus Syndrome, *Radiology* 32: 209-214, 1939.
15. Telihukmacher, N. B.: Surgical Anatomy of the Carotid Sinus Nerve and Inter Carotid Ganglion, *Surg., Gynec. & Obst.* 67: 740-745, 1938.
16. Weese, H.: Mechanism of Anesthesia Accidents Following Intravenous Use of Lipal Soluble, Barbitol Derivative, in Sublingual Phlegmons (Rôle of Carotid Sinus), *Anesth. & Analg.* 18: 15-21, 1939.
17. Weiss, S., and Baker, J.: The Carotid Sinus Reflex in Health and Disease: Its Rôle in Causation of Fainting and Convulsions, *Medicine* 12: 297-354, 1933.
18. Weiss, S., Capps, R. B., Jr., Ferns, E. B., Jr., and Munro, D.: Syncope and Convulsions Due to Hyperactive Carotid Sinus Reflex; Diagnosis and Treatment, *Arch. Int. Med.* 58: 407-417, 1936.

# VITAMIN A CONTENT OF PLASMA AND HEPATIC TISSUE BIOPSIED AT OPERATION: EFFECTS OF PREOPERATIVE THERAPY IN OBSTRUCTIVE JAUNDICE

JOHN D. STEWART, M.D., BUFFALO, N. Y., AND  
G. MARGARET ROURKE, B.A., BOSTON, MASS.

*(From the Surgical Laboratories of the Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts, the Edward J. Meyer Memorial Hospital, Buffalo, New York, and the University of Buffalo Medical School)*

DURING the course of studies on the biochemical changes due to obstruction of the biliary tract, it seemed desirable to investigate possible disturbances in vitamin A metabolism. Abnormalities in vitamin A absorption, conversion, and storage in obstructive jaundice might be predicted on the basis of available evidence.<sup>1, 2</sup> Beta-carotene, the common vegetable source of vitamin A, like vitamin A is fat-soluble and is absorbed from the intestine with difficulty in the absence of bile salts.<sup>2, 3</sup> Beta-carotene and other carotenoid precursors of vitamin A apparently are converted into the vitamin in the liver, through the action of an enzyme, carotinase.<sup>1</sup> As shown in studies on rats, from 90 to 95 per cent of the vitamin A of the body is stored in the liver, small amounts also being found in the kidneys and lungs.<sup>4</sup> Storage of carotene as such occurs to only a negligible extent, however.

Conditions which influence the concentrations of vitamin A and carotenoids in the plasma are not well understood. Bessey and Wolbach<sup>1</sup> concluded that there is no association between the amount of carotene ingested and its level in the plasma. The question has been raised as to whether vitamin A concentration in the plasma reflects the extent of hepatic storage, for fluctuations of the plasma value may occur during acute infections. The weight of evidence seems to indicate, however, that plasma vitamin A concentration in the absence of fever is a satisfactory index of the state of vitamin A nutrition.<sup>5, 6</sup> From observations on sixty-two normal men and the same number of healthy women, Abels and co-workers<sup>7</sup> reported a plasma vitamin A range of 1.32 to 2.08 U.S.P. units per cubic centimeter for the men, and 1.03 to 1.95 for the women, the average figures being 1.70 and 1.49 respectively.

Measurements have been made by various investigators on the vitamin A concentration in the post-mortem hepatic tissue of individuals who died from acute or chronic diseases. The livers of previously healthy individuals succumbing to violence were found to have an average

Presented at the meeting of the Society of University Surgeons, Cincinnati, Ohio, Feb. 12-14, 1942

11. Robinson, L. J.: Syncope, Convulsions and Unconscious State; Relation to Hyperactive Carotid Sinus Reflex, *Arch. Neurol. & Psychiat.* 41: 290-297, 1939.
12. Rovenstine, E. A., and Cullen, S. C.: The Anesthetic Management of Patients With a Hyperactive Carotid Sinus Reflex, *SURGERY* 6: 167-176, 1939.
13. Smith, H. L.: Fainting Attacks Resulting From Hypersensitive Carotid Sinus Reflexes, *Am. Heart J.* 14: 614-619, 1937.
14. Stevenson, C. A.: Use of Roentgen Therapy in Carotid Sinus Syndrome, *Radiology* 32: 209-214, 1939.
15. Tchibukmacher, N. B.: Surgical Anatomy of the Carotid Sinus Nerve and Inter-Carotid Ganglion, *Surg., Gynec. & Obst.* 67: 740-745, 1938.
16. Weese, H.: Mechanism of Anesthesia Accidents Following Intravenous Use of Evipal Soluble, Barbitol Derivative, in Sublingual Phlegmons (Rôle of Carotid Sinus), *Anesth. & Analg.* 18: 15-21, 1939.
17. Weiss, S., and Baker, J.: The Carotid Sinus Reflex in Health and Disease: Its Rôle in Causation of Fainting and Convulsions, *Medicine* 12: 297-354, 1933.
18. Weiss, S., Capps, R. B., Jr., Ferris, E. B., Jr., and Munro, D.: Syncope and Convulsions Due to Hyperactive Carotid Sinus Reflex; Diagnosis and Treatment, *Arch. Int. Med.* 58: 407-417, 1936.

## METHODS

Of the various modifications of the Carr-Price antimony trichloride reaction for the determination of vitamin A and carotene in the plasma, the method as described by McCoord and Luce-Clausen was used.<sup>12</sup> Vitamin A values are expressed in U.S.P. units per cubic centimeter, while plasma carotenoids values are given as U.S.P. units of equivalent vitamin A. Vitamin A concentration in the biopsied liver tissue was measured by Moore's technique.<sup>11</sup> Hepatic biopsy was performed at

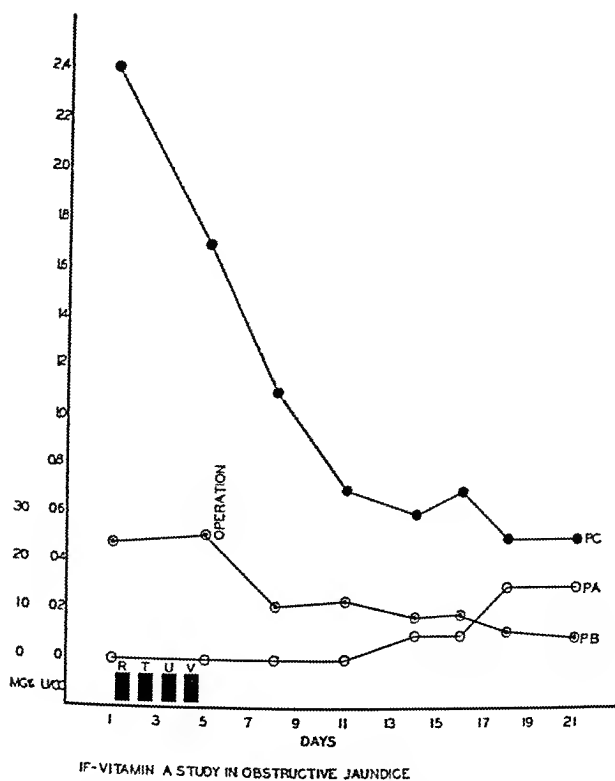


Fig. 2—I. F., a 65-year-old woman with stones in the gall bladder and common duct and severe jaundice, had cholecystectomy and choledochostomy performed under ether anesthesia; jaundice cleared gradually after operation. Vitamin A, 500,000 U.S.P. units, was given intramuscularly at points R, T, U, and V. PA indicates plasma vitamin A concentration in U.S.P. units per cubic centimeter, PC indicates plasma carotenoids concentration expressed as U.S.P. vitamin A units per cubic centimeter, while PB equals plasma bilirubin concentration in milligrams per 100 c.c. Hepatic tissue biopsied at operation contained 91 U.S.P. units of vitamin A per gram.

operation by taking a wedge-shaped piece of tissue from the anterior margin of the right lobe between hemostatic stitches. The specimens weighed from 0.5 to 1.5 Gm. and the validity of this method of sampling has been tested and described.<sup>13</sup> In no instance was hemorrhage or bile leakage observed in consequence of the biopsy. In some cases hepatic biopsy was performed early and again late in the course of the operation

vitamin A content of 331 U.S.P. units per gram, according to Crimm and Short.<sup>8</sup> Ralli and collaborators<sup>9</sup> reported an average value from similar material of 766 U.S.P. units per gram, with a rather wide variation noted. They found much lower concentrations in cirrhotic livers, the average value being 137 U.S.P. units per gram, and in acute infections accompanied by evidence of liver damage. Fox<sup>10</sup> found concentrations of 12 to 938 "blue units" per gram of liver tissue in native mine workers killed in industrial accidents, the average figure being 297. Similar values were recorded by Moore.<sup>11</sup> All such studies have shown wide variation in the post-mortem hepatic vitamin A content, even in the livers of individuals supposedly in good health prior to fatal trauma.

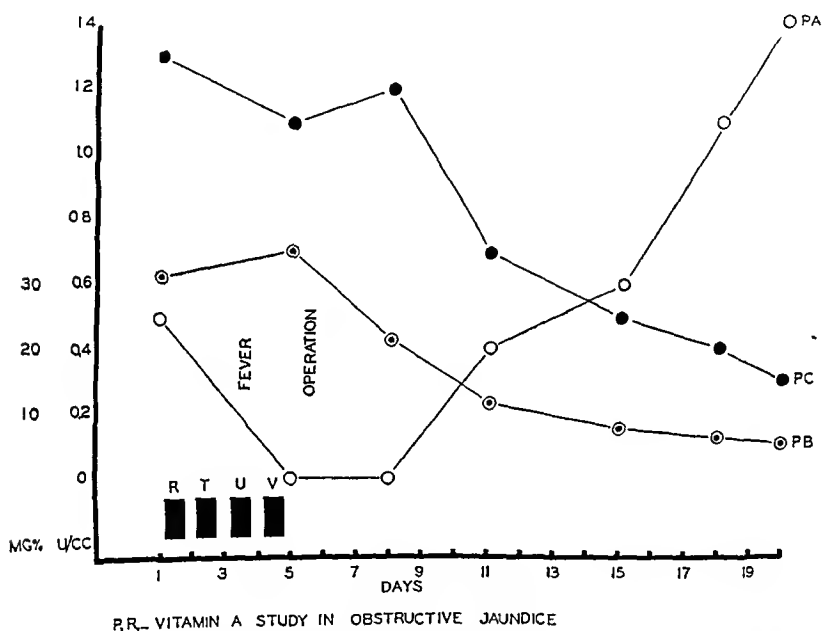
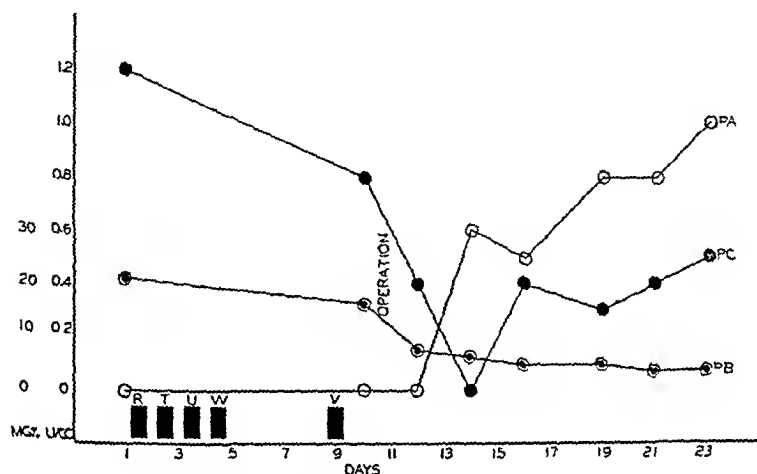


Fig. 1.—P. R., a 60-year-old man with carcinoma of the head of the pancreas and complete biliary obstruction, had cholecystogastrostomy performed under spinal anesthesia, after which the jaundice rapidly cleared. Before operation, at points marked R, T, U and V, daily intramuscular injections of 500,000 units of vitamin A in corn oil were given him. PA indicates plasma vitamin A concentration in U.S.P. units per cubic centimeter, PC indicates plasma carotenoids concentration in equivalent U.S.P. vitamin A units, while PB indicates plasma bilirubin concentration in milligrams per 100 cc. Hepatic vitamin A concentration in the sample biopsied at operation equaled 1,500 U.S.P. units per gram.

In the present study an effort was made to determine the relationship, if any, between plasma vitamin A and carotenoids concentrations, and concentration of vitamin A in hepatic tissue removed by biopsy during surgical operation. The effects of administering vitamin A intramuscularly and of giving carotene and deoxycholeic acid orally to patients with obstructive jaundice were observed, in relation to surgical release of biliary obstruction and subsidence of jaundice.

the plasma vitamin A value was zero, and in four cases vitamin A could not be detected in the hepatic sample. These data demonstrate that in obstructive jaundice the plasma may contain no vitamin A, even though the concentration of plasma carotenoids is within normal limits, and vitamin A is present in the liver.



MS-VITAMIN A STUDY IN OBSTRUCTIVE JAUNDICE

Fig. 3.—M. S., a 36-year-old man with carcinoma of the head of the pancreas, severe jaundice, and diabetes mellitus, had cholecystgastrostomy done under spinal anesthesia, after which the jaundice subsided rapidly and insulin requirements abruptly declined. At points marked R, T, U, W, and V daily intramuscular injections of vitamin A, 500,000 U.S.P. units each, were given. PA indicates plasma vitamin A concentration in U.S.P. units per cubic centimeter, PC indicates plasma carotenoids concentration expressed as U.S.P. units of vitamin A per cubic centimeter, while PB indicates plasma bilirubin concentration in milligrams per 100 cc. Vitamin A concentration in hepatic biopsy sample taken at operation was 353 U.S.P. units per gram.

TABLE II

PLASMA AND HEPATIC VITAMIN A VALUES IN PATIENTS WITH OBSTRUCTIVE JAUNDICE NOT RECEIVING VITAMIN A BEFORE OPERATION

CASE	PLASMA		HEPATIC VITAMIN A UNITS PER GM.
	CAROTENOIDS UNITS PER C.C.	VITAMIN A UNITS PER C.C.	
F. D.	1.1	0	57
F. H.	3.2	0	0
M. B.	1.9	0	79
J. S.	2.3	0	56
M. C.	0.4	0	0
M. K.	1.9	0	307
B. D.	1.6	0	312
E. Z.			0
E. B.	0.6	0	0
Average	1.6	0	90

By contrast, Table III presents the data from patients who had received large doses of vitamin A or carotene before operation. The first eight patients in the table received 500,000 U.S.P. units of vitamin A intramuscularly for three or four days immediately before opera-

on the biliary tract. The vitamin A preparation\* given parenterally consisted of vitamin A in corn oil, and contained 500,000 U.S.P. units of vitamin A per cubic centimeter. Carotene was administered orally as beta-carotene in cottonseed oil, the material used having a potency equivalent to 7,500 U.S.P. units of vitamin A per gram.†

TABLE I

PLASMA AND HEPATIC VITAMIN A VALUES IN PATIENTS WITH CHRONIC CHOLECYSTITIS, WITH OPERATION UNDER ETHER ANESTHESIA

Vitamin A not given before operation

CASE	PLASMA		HEPATIC VITAMIN A UNITS PER GM.
	CAROTENOIDS UNITS PER C.C.	VITAMIN A UNITS PER C.C.	
L. L.	2.5	1.0	486
M. M.	2.9	1.7	109
L. M.	2.4	0.5	300
A. D.	0.9	1.1	35
P. H.	1.3	1.1	52
J. V.	1.5	1.0	33
M. S.	1.0	0.9	148
A. B.	0.8	0.6	74
E. M.	0.6	0.8	352
B. B.	1.2	1.2	417
M. S.	1.4	1.3	428
M. L.	1.0	0.2	25
I. F.	1.3	1.4	533
Average	1.5	0.98	230

#### PRESENTATION OF DATA, AND COMMENT

In Table I are shown values for concentration of carotenoids and vitamin A in the plasma and vitamin A in liver biopsy specimens from a group of thirteen patients undergoing cholecystectomy for chronic cholecystitis. Blood samples were taken just before induction of ether anesthesia, and hepatic biopsy was performed immediately after the peritoneal cavity was opened. The patients were without evidence of active infection at the time. These data serve as control values in interpreting the findings in patients with jaundice and liver damage. The wide range in plasma and hepatic vitamin A values is noteworthy. Dark adaptation measurements were not made in this study, and although these patients presented no symptoms or objective evidence of vitamin A lack, it is not certain that subclinical deficiency may not have been present in some instances.

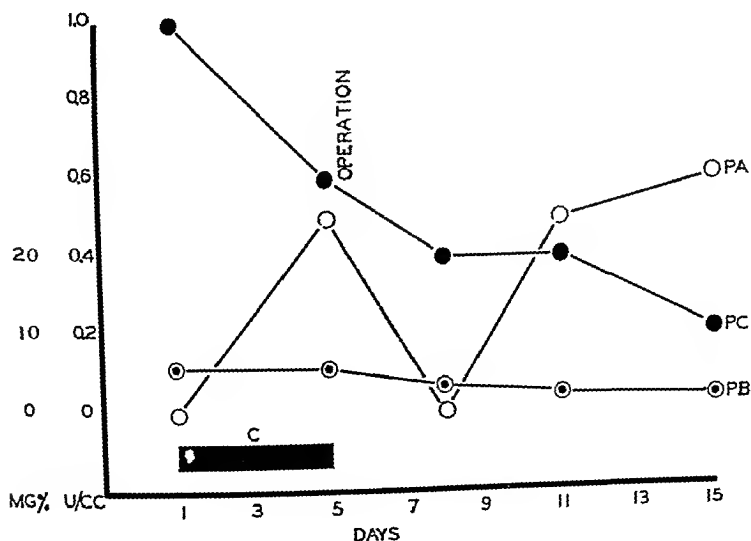
In Table II are shown results of similar analyses in a group of nine patients with obstructive jaundice of high degree. No carotene or vitamin A had been given the patients preoperatively. Again, considerable fluctuation is noted in the plasma carotenoids, but in every case

\*Kindly prepared by Dr. A. Black, of the Biological Laboratories of E. R. Squibb & Sons.

†Deoxycholeic acid for oral use was supplied by Riedel-de Haen, Inc.

effect on plasma values of carotenoids and vitamin A is seen as a result of such treatment. However, though much variation in hepatic vitamin A content is evident, hepatic storage of the vitamin is clearly visible. As shown in case P. R., under these conditions very high concentration of vitamin A may be present in the liver while the plasma concentration is still zero.

The data of Table IV suggest two conclusions. Lengthy operation on the biliary tract under ether anesthesia apparently produces little or no change in hepatic vitamin A concentration. Furthermore, the validity of the sampling method is supported by the finding of similar vitamin A values in the specimens taken at the beginning, and again at the end, of the operation.



L.B.- VITAMIN A STUDY IN OBSTRUCTIVE JAUNDICE

Fig 5—L. B., an obese, elderly, mildly jaundiced woman was found to have a stone impacted at the papilla of Vater which was removed under ether anesthesia by choledochostomy and duodenotomy. Before operation during the period marked C, 8 Gm of carotene in cottonseed oil and 1 Gm of deoxycholeic acid were given orally each day, the vitamin A equivalent per day being 60,000 U.S.P. units. PA indicates plasma vitamin A concentration in U.S.P. units per cubic centimeter, PC indicates plasma carotenoids concentration expressed as U.S.P. units of vitamin A per cubic centimeter, and PB indicates plasma bilirubin concentration in milligrams per 100 c.c. Vitamin A concentration in hepatic tissue biopsied at operation was 118 U.S.P. units per gram.

In Figs. 1, 2, 3, 4, 5, and 6 are shown values for concentration of vitamin A, carotenoids, and bilirubin in the plasma, before and after operation. Vitamin A, or carotene, was administered before operation. In one patient, as shown in Fig. 3, inoperable obstruction to the hepatic ducts was encountered and death resulted from liver failure and pneumonia ten days after operation. In this case the plasma vitamin A value remained zero despite the fact that a total of 2,000,000 U.S.P. units had



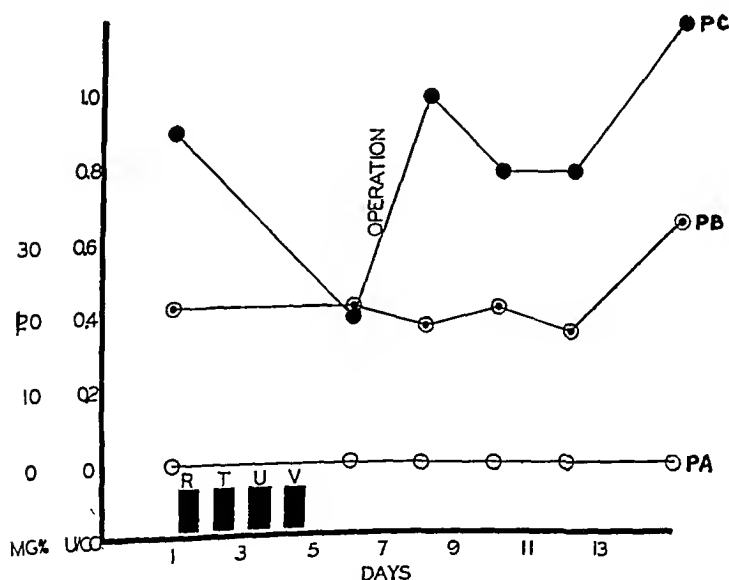
TABLE III

PLASMA AND HEPATIC VITAMIN A VALUES IN PATIENTS WITH OBSTRUCTIVE JAUNDICE

CASE	PLASMA		HEPATIC VITAMIN A UNITS PER GM.
	CAROTENOIDS UNITS PER C.C.	VITAMIN A UNITS PER C.C.	
F. H.	1.0	0	688
E. S.	0.8	0.5	750
P. R.	1.1	0	1500
L. C.	0.4	0	136
M. S.	0.8	0	353
I. F.	1.7	0	91
A. S.	0.5	0	50
J. C.	1.2	0.2	115
R. M.*	3.6	0.9	417
W. W.*	2.5	1.2	344
L. B.*	0.6	0.5	118
Average	1.3	0.3	413

\*These patients had received beta-carotene and deoxycholeic acid orally; the rest had received vitamin A parenterally.

tion. The last three patients were given 8 Gm. of beta-carotene in oil (vitamin A equivalent total 60,000 U.S.P. units) and 1 Gm. of deoxycholeic acid daily for three to five days before operation. No striking



LC.- VITAMIN A STUDY IN OBSTRUCTIVE JAUNDICE

Fig. 4.—L. C., a 59-year-old woman with gallstones and inoperable carcinoma of the hepatic ducts and liver, jaundice not relieved by operation under ether anesthesia, died of liver failure and pneumonia ten days after operation. At points R, T, U, and V vitamin A was injected intramuscularly in doses of 500,000 U.S.P. units daily. PC indicates plasma carotenoids concentration expressed as U.S.P. units of vitamin A per cubic centimeter, PA indicates plasma vitamin A concentration in U.S.P. units per cubic centimeter, and PB indicates plasma bilirubin concentration in milligrams per 100 c.c. Concentration of vitamin A in hepatic tissue biopsied at operation was 136 U.S.P. units per gram.

theless the plasma value returned to normal only with subsidence of jaundice postoperatively, and improvement in liver function.

In two patients, L. B. as shown in Fig. 5, and R. M. as shown in Fig. 6, plasma vitamin A was reduced at the time of operation but not entirely absent, and it is of interest that further decrease occurred immediately after operation. This event suggests the parallel finding of postoperative decrease in plasma prothrombin in patients with obstructive jaundice<sup>14</sup> and supplies further evidence of the importance of hepatic function in the regulation of plasma vitamin A level.

The data appearing in the illustrations demonstrate that concentrations of plasma vitamin A and plasma carotenoids tend to vary inversely, a point which is particularly well shown in Fig. 1. Vitamin A and carotene were not given the patients postoperatively, and the decline in plasma carotenoids possibly depends on more rapid conversion of the provitamin with improvement in liver function.

#### SUMMARY

Concentrations of vitamin A and carotenoids in the plasma, and concentration of vitamin A in biopsied liver samples have been determined in the following groups of patients:

1. Thirteen patients undergoing cholecystectomy for chronic cholecystitis and cholelithiasis, without jaundice or evidence of active infection, and not given vitamin A preoperatively.
2. Nine patients undergoing operation for obstructive jaundice of high degree and not given vitamin A preoperatively.
3. Eight patients undergoing operation for obstructive jaundice after receiving large doses of vitamin A parenterally.
4. Three patients operated upon for obstructive jaundice after receiving carotene and deoxycholeic acid orally.

In six patients the liver was biopsied at the beginning and again at the end of operation on the biliary tree under ether anesthesia.

Plasma concentrations of vitamin A, carotenoids, and bilirubin were repeatedly determined before and after operation and are presented graphically from five cases in which biliary obstruction was relieved by operation, and in one case of inoperable carcinoma of the hepatic ducts.

#### CONCLUSIONS

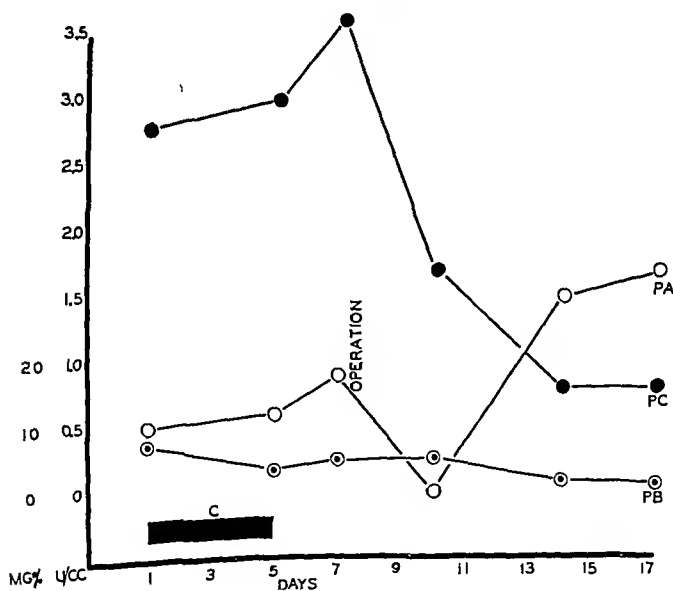
1. Concentrations of vitamin A and carotenoids in the plasma, and concentrations of vitamin A in the liver vary considerably in patients with chronic cholecystitis, but a rough correlation between plasma and hepatic vitamin A content is evident.
2. In patients with obstructive jaundice not given vitamin A, plasma vitamin A values of zero are common, though plasma concentrations of carotenoids may be normal. Vitamin A values in biopsied liver tissue likewise may be zero.

been administered intramuscularly before operation. Since the biopsied hepatic tissue at operation contained vitamin A, the findings in this case suggest that plasma vitamin A concentration may be decreased as a result of impaired liver function, regardless of the presence of vitamin A in the liver. The data shown graphically in Fig. 1 offer further support to this conception, for despite the extremely high vitamin A content of the liver at operation, that is, 1,500 units per gram, never-

TABLE IV

EFFECT OF OPERATION AND ETHER ANESTHESIA ON HEPATIC VITAMIN A CONCENTRATION IN OBSTRUCTIVE JAUNDICE

CASE	INITIAL HEPATIC VITAMIN A UNITS PER GM.	FINAL HEPATIC VITAMIN A UNITS PER GM.	DURATION OF OPERATION IN MINUTES
A. S.	50	50	80
J. C.	115	125	70
W. W.	334	278	50
M. K.	307	312	75
R. D.	271	250	140
I. F.	91	68	140



R. M.—VITAMIN A STUDY IN OBSTRUCTIVE JAUNDICE

Fig 6—R. M., a 57-year-old man with stones in the gall bladder and common duct and mild jaundice had cholecystectomy and choledochostomy performed under ether anesthesia, followed by uneventful convalescence. During the period marked C, 8 Gm of carotene in cottonseed oil and 1 Gm of dextrochole acid were given orally each day, the vitamin A equivalent per day being 60,000 USP units. PA indicates plasma vitamin A concentration in USP units per cubic centimeter. PC indicates plasma carotenoids concentration expressed as USP units of vitamin A per cubic centimeter, and PB indicates plasma bilirubin concentration in milligrams per 100 cc. Vitamin A concentration in hepatic tissue biopsied at operation was 317 USP units per gram.

# THE VALUE OF SKIN RESISTANCE STUDIES IN DETERMINING THE ACCURACY OF PROCAINE INJECTIONS OF THE SYMPATHETIC NERVES

HARRIS B. SHUMACKER, JR., M.D., BALTIMORE, MD.

*(From the Department of Surgery, the Johns Hopkins University)*

PROCAINE injection of the sympathetic nerves has become an invaluable aid in the study of the peripheral circulation and in the treatment of certain vascular disorders. These injections are made after the skin temperature of the affected limb has become stabilized through exposure to cold. If following the attempted sympathetic block there occurs a substantial increase in the skin temperature of the affected limb, not only is a significant element of vasospasm and a good capacity of the vascular bed for dilatation demonstrated, but the efficacy of the procaine injection is proved. If, on the other hand, little or no elevation in skin temperature takes place, the question always arises as to whether the circulatory difficulty is entirely due to obliterative arterial disease with no significant element of vascular spasm, or whether the operator has failed to achieve a satisfactory anesthesia. In the study of the upper extremities this question may be settled by the presence of a Horner's syndrome, but there is no similarly helpful sign in the study of the lower extremities, in which almost all the cases of severe obliterative arterial disease occur. There are, furthermore, occasions for therapeutic procaine injection or for procaine block preliminary to alcohol injection when it is either not necessary or perhaps even undesirable to expose the affected part to a cold room temperature. It is apparent that any method which might help in determining the accuracy of sympathetic injections would be a useful adjunct.

It has been known for some time that the resistance of the skin to passage of a small electric current is very high in areas in which sympathetic denervation has been brought about by operation.<sup>1</sup> Dr. C. P. Richter has been very helpful in outlining the denervated area in most of the patients whom I have subjected to sympathectomy, and a definite correlation has been found between the area of high skin resistance and the level and extent of the operative procedure.<sup>1</sup> Similar changes are present after chemical section of the sympathetics by means of alcohol injection. It occurred to me that the same changes would probably be present during the period of sympathetic anesthesia following procaine injection and that these studies would be helpful in determining whether an injection resulted in successful sympathetic paralysis.

<sup>1</sup>Presented at the meeting of the Society of University Surgeons, Cincinnati, Ohio, Feb. 12-14, 1942.

3. Administration of large amounts of vitamin A parenterally, or carotene and deoxycholeic acid orally before operation in patients with obstructive jaundice is followed by the finding of normal vitamin A values in the biopsied liver specimen; rise in plasma vitamin A concentration, however, occurs more slowly, and may depend on improvement in liver function as produced by release of biliary obstruction.

4. Hepatic vitamin A concentration does not appear to change significantly during the course of operations on the biliary tract under ether anesthesia; postoperative reduction in plasma vitamin A concentration, however, is to be expected.

#### REFERENCES

1. Bessey, O. A., and Wolbach, S. B.: Vitamin A: Physiology and Pathology. The Vitamins, Chicago, 1939, American Medical Association.
2. Greaves, J. D., and Schmidt, C. L. A.: On the Absorption and Utilization of Carotene and Vitamin A in Choleodochocolonostomized Vitamin A Deficient Rats, *Am. J. Physiol.* **111**: 492, 1935.
3. Altschule, M. D.: Vitamin A Deficiency in Spite of Adequate Diet in Congenital Atresia of Bile Ducts and Jaundice, *Arch. Path.* **20**: 845, 1935.
4. Baumann, C. A., Riising, B. M., and Steenbock, H.: The Absorption and Storage of Vitamin A in the Rat, *J. Biol. Chem.* **107**: 705, 1934.
5. May, C. D., Blackfan, K. D., McCreary, J. F., and Allen, F. H., Jr.: Clinical Studies of Vitamin A in Infants and in Children, *Am. J. Dis. Child.* **59**: 1167, 1940.
6. Steininger, G., Roberts, L. J., and Brenner, S.: Vitamin A in the blood of Normal Adults: The Effect of a Depletion Diet on Blood Values and Biophotometer Readings, *J. A. M. A.* **113**: 2381, 1939.
7. Abels, J. C., Gorham, A. T., Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients With Cancer of the Gastrointestinal Tract. I. Plasma Vitamin A Levels in Patients With Malignant Neoplastic Disease, Particularly of the Gastrointestinal Tract, *J. Clin. Investigation* **20**: 749, 1941.
8. Crimm and Short: Quoted by Ralli, Papper, Paley, and Baumann.
9. Ralli, E. P., Papper, E., Paley, K., and Baumann, E.: Vitamin A and Carotene Content of Human Liver in Normal and in Diseased Subjects: An Analysis of 116 Human Livers, *Arch. Int. Med.* **68**: 102, 1941.
10. Fox, F. W.: Vitamin A in the Livers of Native Mine Workers With Special Reference to Their Resistance to Pneumonia, *Lancet* **1**: 953, 1933.
11. Moore, T.: Vitamin A and Carotene: the Vitamin A Reserve of the Adult Human Being in Health and Disease, *Biochem. J.* **31**: 155, 1937.
12. McCoord, A. B., and Luce-Clausen, Ethel, M.: The Storage of Vitamin A in the Liver of the Rat, *J. Nutrition* **7**: 557, 1934.
13. Rourke, G. M., and Stewart, J. D.: On the Uniformity of Hepatic Composition With Respect to Concentration of Certain Biochemical Constituents in Different Parts of the Same Liver, *Arch. Path.* In press.
14. Stewart, J. D.: Prothrombin Deficiency and the Effects of Vitamin K in Obstructive Jaundice and Biliary Fistula, *Ann. Surg.* **109**: 588, 1939.

obtaining sympathetic anesthesia, as evidenced by failure to obtain a rise in skin temperature after the injection, and subsequent demonstration of a fairly good capacity of the vascular bed for vasodilatation by other observations, including operative sympathectomy. This failure of sympathetic anesthesia was obvious because there was not the characteristic unilateral increase in cutaneous resistance which was observed in

TABLE I

CUTANEOUS RESISTANCE BEFORE AND AFTER ATTEMPTED SYMPATHETIC ANESTHESIA

NO.	NAME	CUTANEOUS RESISTANCE IN OHMS					TYPE OF INJECTION
		POINT	BEFORE INJECTION		AFTER INJECTION		
			RIGHT	LEFT	RIGHT	LEFT	
1	E. M.	Dorsum Palm	1,500,000 350,000	2,800,000 900,000	1,000,000 220,000	T.H. T.H.	Left dorsal
2	M. M.	Dorsum Palm	350,000 100,000	330,000 540,000	1,900,000 T.H.	210,000 500,000	Right dorsal
3	M. B.	Dorsum Palm	160,000 T.H.	150,000 T.H.	130,000 270,000	500,000 3,350,000	Left dorsal
4	C. B.	Dorsum Palm	T.H. 100,000	T.H. 140,000	T.H. T.H.	T.H. 400,000	Right dorsal
5	C. F.	Dorsum Sole	350,000 300,000	700,000 190,000	950,000 200,000	T.H. 1,000,000	Left lumbar
6	D. F.	Dorsum Sole	390,000 1,300,000	570,000 1,200,000	290,000 1,100,000	T.H. T.H.	Left lumbar
7	I. R.	Dorsum Sole	3,500,000 600,000	3,100,000 300,000	T.H. T.H.	200,000 300,000	Right lumbar
8	F. N.	Dorsum	700,000	500,000	1,400,000	T.H.	Left lumbar
9	S. G.	Dorsum Sole	390,000 410,000	300,000 510,000	T.H. T.H.	310,000 390,000	Right lumbar
10	I. R.	Dorsum Sole	720,000 1,700,000	330,000 1,500,000	T.H. 650,000	460,000 460,000	Right lumbar
11	C. B.	Dorsum Sole	300,000 500,000	250,000 980,000	530,000 690,000	T.H. T.H.	Left lumbar
12	G. C.	Dorsum Sole	2,400,000 2,700,000	1,600,000 1,750,000	T.H. T.H.	1,450,000 1,200,000	Right lumbar
13	R. B.	Dorsum Sole	890,000 600,000	950,000 500,000	T.H. T.H.	1,000,000 400,000	Right lumbar
14	R. M.	Dorsum Sole	520,000 890,000	500,000 520,000	540,000 890,000	1,100,000 2,100,000	Left lumbar
15	L. S.	Dorsum Sole	790,000 3,000,000	900,000 2,800,000	T.H. T.H.	1,950,000 2,100,000	Right lumbar
16	F. C.	Dorsum Sole	1,700,000 600,000	1,200,000 500,000	T.H. 3,250,000	2,000,000 480,000	Right lumbar
17	P. E.	Dorsum Sole	1,100,000 T.H.	400,000 450,000	1,600,000 T.H.	T.H. 2,000,000	Left lumbar
18	M. H.	Dorsum Sole			1,300,000 2,000,000	T.H. T.H.	Left lumbar
19	F. D.	Dorsum Sole	160,000 580,000	160,000 600,000	1,400,000 T.H.	600,000 1,650,000	Left lumbar
20	T. S.	Dorsum Sole Leg*	T.H. T.H. 1,500,000	T.H. T.H. 1,000,000	T.H. T.H. 1,000,000	T.H. T.H. T.H.	Left lumbar
21	R. C.	Dorsum Sole	191,000 750,000	430,000 490,000	2,900,000 T.H.	T.H. T.H.	Spinal (Ponto- caine 10 mg.)

\*These readings were made with kaolin paste on the electrode.

## METHOD AND EXPERIMENTAL OBSERVATIONS

The limbs to be studied were exposed in a cool room, generally about 20° C., until the skin temperature had become stable. During this period a number of observations of cutaneous resistance were made with a machine similar to that described by Levine.<sup>1, 2</sup> This machine permits one to measure the current passed through the skin and the number of ohms resistance offered by the skin to passage of the current. A zinc electrode covered with kaolin paste is fixed to the lobe of one ear at a site where the skin has been punctured with a needle. The other zinc electrode is applied to the skin of the limbs being studied. The operator becomes adept in holding the electrode against the skin with approximately the same amount of pressure and for approximately the same interval of time during each reading. The potentiometer knobs are turned until the galvanometer which serves as an ammeter registers passage of exactly two microamperes. The other galvanometer, which is used as a voltmeter and which measures the voltage necessary to send through this amperage, is calibrated so that the number of ohms resistance can be read directly. Accurate observations of skin resistance can be made up to 3,800,000 or 4,000,000 ohms. Higher values cannot be read accurately and in the records and figures are recorded as too high to be read (T. H.). At least one point on the dorsum and one on the palm or sole were selected for reading in each patient, the points being the same on both hands or both feet. These sites for resistance readings were selected where the resistance was not high, and in order to obviate inadvertent change in the point of reading, each was marked with a skin pencil. Generally the needles through which the procaine was injected were left in place until the skin resistance in the ipsilateral hand or foot had begun to increase substantially, indicating that an effectual block was being accomplished.

Studies were made upon twenty-one subjects. These were patients with various types of peripheral vascular disorders: Raynaud's disease, Raynaud's disease and arthritis, Buerger's disease associated with varying degrees of vasospasm, peripheral arteriosclerosis with and without accompanying vascular spasm, acute thrombophlebitis, thrombophlebitic sequelae, traumatic reflex edema and causalgia, and vasospasm and calcinosis. Four patients subjected to upper dorsal sympathetic blocks, sixteen to lumbar sympathetic blocks, and one to spinal anesthesia were studied. In Table I are recorded the skin resistance values before injection and at a time after injection when the difference between the two limbs was maximal. In every instance the study of cutaneous resistance was helpful in determining whether the injection produced satisfactory anesthesia. All injections except one were successful and were accompanied by marked rise in skin resistance on the side on which the injection was made. In one case (Case 1<sup>st</sup>) the operator was unsuccessful in

Fig. 3 is shown for comparison a chart of the changes in skin temperature and skin resistance after spinal anesthesia in a young man with recurrent migrating phlebitis and vasospasm. In all three instances the rise in skin temperature of the ipsilateral foot was adequate evidence of the efficacy of the sympathetic injection. In Fig. 4, however, the record is charted of a patient in whom it would have been impossible without the skin resistance studies to know whether a good sympathetic block had been obtained. The failure of the skin temperature to rise

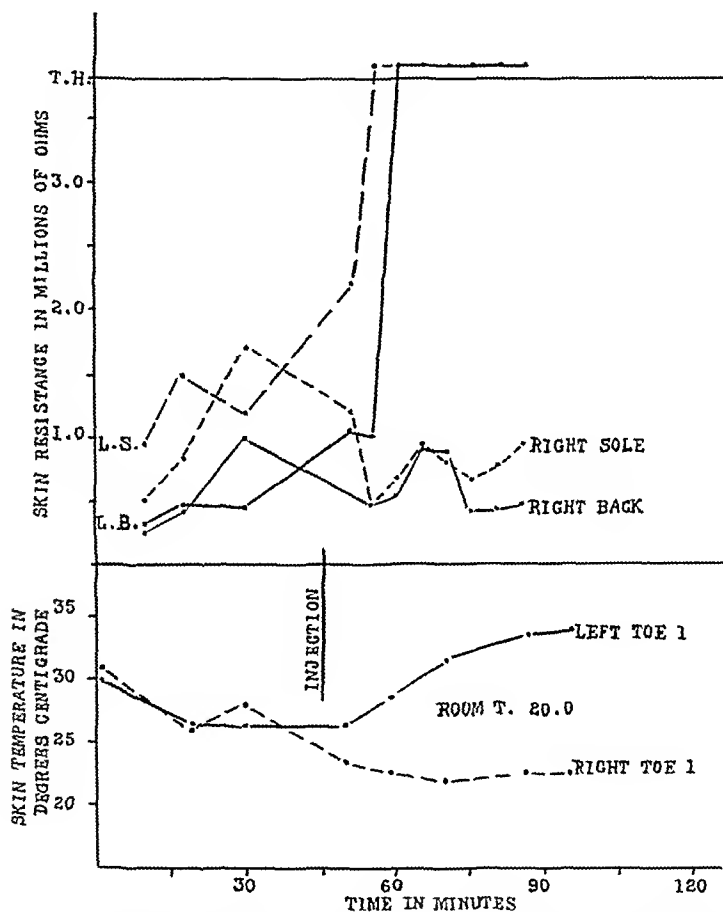


Fig. 2—Chart showing rise in skin resistance and skin temperature in the ipsilateral foot following left lumbar sympathetic block. Case 11. Peripheral arteriosclerosis and peripheral neuritis.

significantly might have been due to the inability of the vascular bed to dilate, or it might have been due to failure in producing successful sympathetic paralysis. The prompt increase in skin resistance on the injected side gave convincing proof that the former was the case. In this series there were a number of other instances in which little or no rise



all other instances. In each patient subjected to a dorsal block distinct Horner's syndrome occurred as well as prompt and significant rise in both skin resistance and skin temperature.

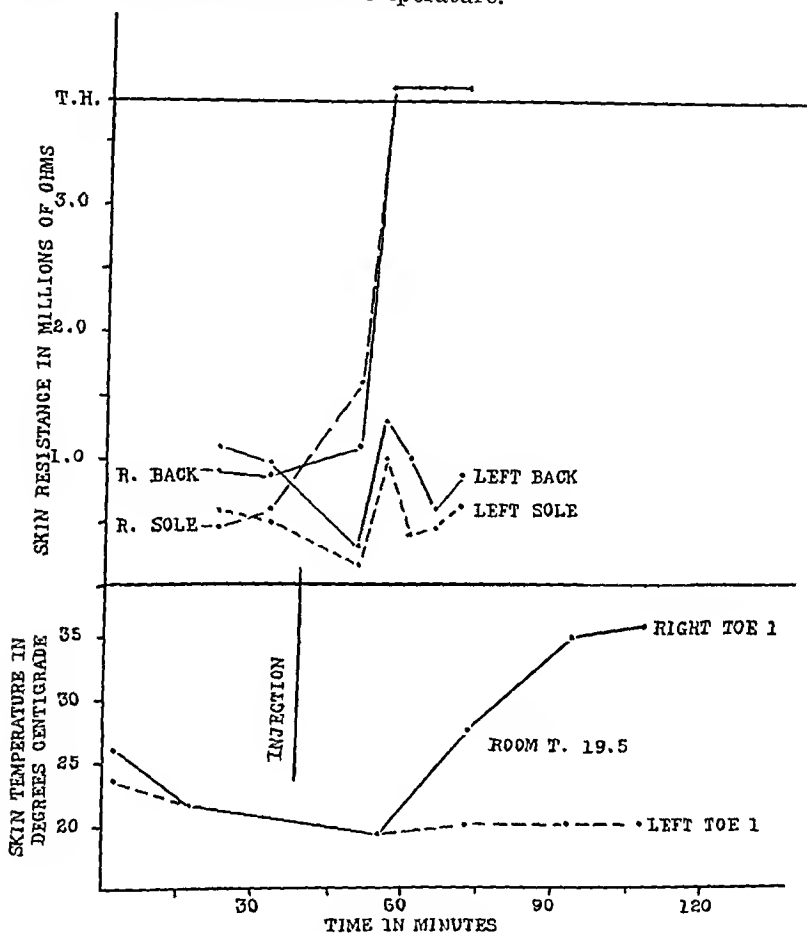


Fig. 1.—Chart showing rise in skin resistance and skin temperature in the ipsilateral foot following right lumbar sympathetic block (Case 13) Postphlebotic ulceration, edema, and vasospasm.

In Figs. 1 and 2 are charted the changes in skin resistance and in skin temperature in two patients who showed the customary increase in skin resistance following procaine block of the lumbar sympathetics and who also responded with increased warmth in the foot.\* One was a patient with postphlebotic edema, ulceration, and vasospasm, the other a patient with peripheral arteriosclerosis and peripheral neuritis. In

\*In these and in the other cases charted, changes in the temperature of only a single digit on each side are recorded, for the sake of simplicity. In all cases, however, several digits of each hand or foot are always studied. In addition I always record temperature changes on the soles of the feet. I feel that such multiple readings are very important. Sometimes there will be no rise in temperature of the great toe whereas there will be an excellent response in the other toes and the sole. If only the great toe were studied one might conclude that no improvement could be expected from sympathectomy when as a matter of fact decided improvement could be anticipated.

demonstration of the unilateral increase following effectual sympathetic block. Generally the initial skin resistance in both feet or both hands, and the final values on the uninjected side were relatively low compared with the very high values present after sympathetic anesthesia was obtained. Occasionally the values were rather high, as in Cases 12 and 15, but still the differences after sympathetic injection were striking. Sometimes when the initial values were rather high, as in Case 7, as the

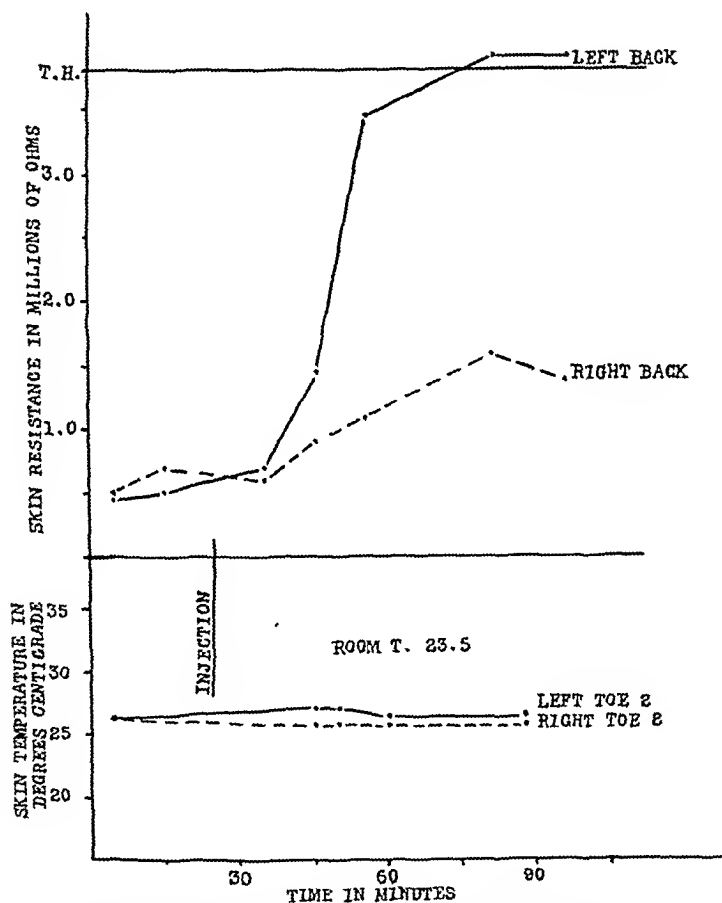


Fig 4—Chart showing rise in skin resistance in the ipsilateral foot following left lumbar sympathetic block in a patient in whom there was no increase in skin temperature. Case 8 Diabetes, arteriosclerosis, gangrene of toe

study progressed the skin resistance in the unanesthetized limb fell in such a way as to make the differences very great. In Case 17 the skin resistance remained rather high on the back of the right foot and too high to read on the right sole. The low skin resistance on the left foot, however, gave way to very high values after left lumbar sympathetic block was accomplished, and there was no difficulty in interpreting the

in skin temperature occurred and in which, without the resistance studies, one would have wondered whether the sympathetic block had been completely or partly ineffectual.

The resistance of the normally innervated skin is lowest when the patient has been warmed by exposure of the body in a hot-air cabinet and when sweating is active; it is much higher when the body is cold. For this reason the skin resistance studies which are carried out on

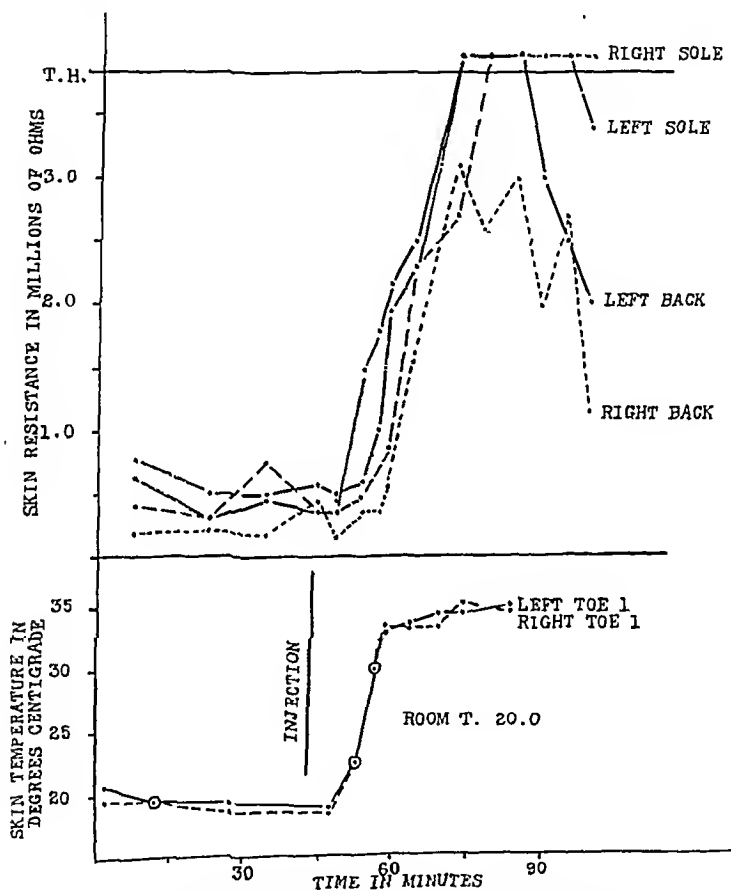


Fig. 3.—Chart showing rise in skin resistance and skin temperature in the foot following spinal anesthesia (10 mg. pontocaine). Case 21. Migrating phlebitis and vasospasm.

sympathectomized patients have been done immediately after the patient has been heated in a cabinet. With such preparation any abnormally high skin resistance is more significant and the affected area can be more sharply outlined because the resistance in the normally innervated areas is so low. When the present investigation was begun this matter afforded me some concern, for I was not sure whether the skin resistance in a patient exposed to cold would be sufficiently low to permit a clear-cut

It has been my feeling that the more accurately the tips of the needles are placed in close proximity to the sympathetic ganglia, the quicker the occurrence of the rise in skin temperature in the hand or foot, and I believe that in general this is the correct explanation. Occasionally, however, the rise in skin temperature is extremely tardy\* and such occur-

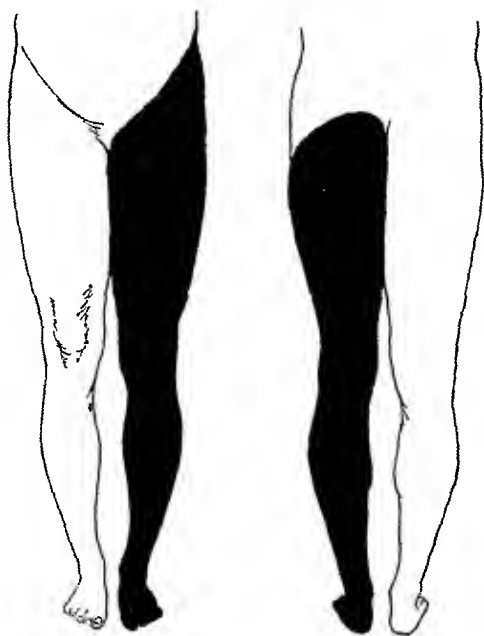


Fig 5.—Showing the area of high skin resistance in the ipsilateral extremity following left lumbar sympathetic block. The shaded area represents the area in which the skin resistance was too high to read Case 18. Arteriosclerosis, left popliteal thrombosis.

rences have been very puzzling to me. Case 9, which is charted in Fig. 6, is an interesting example. It will be seen from the rapid and significant rise in cutaneous resistance that the sympathetic injection was made accurately and that prompt anesthesia resulted. It was almost an hour, however, before any rise in skin temperature occurred. Once this began the temperature rose rapidly to a normal level. Operative sympathectomy was similarly followed by great increase in warmth. Why there should be such a long delay in the rise in temperature of the foot after effective sympathetic anesthesia I cannot say. It is hoped that additional observations of similar reactions may throw some light upon this interesting problem. It should be noted that there is generally a lag of some minutes in the beginning of rise in skin temperature after the skin resistance has begun to increase, as is to be expected since increased heat is an effect of vasodilatation and not an instantaneous reaction.

\*For this reason I always make observations of temperature for at least an hour after injection, even when no increase occurs.

resistance studies as indicative of an effectual block. During the sympathetic anesthesia in this case the dorsum of each foot was explored extensively with the electrode. Only one point was found on the left foot where the skin resistance was low enough to permit one to obtain a reading, whereas the values on the unanesthetized right dorsum were everywhere low enough for reading. In Case 4 the resistance of the dorsal surface of both hands was too high to be read, but study of the resistance of the palms gave adequate information. Similarly in Case 8, the skin resistance on the soles of both feet was too high to read, but satisfactory information could be derived from measurements on the dorsum (Fig. 4). Only in one instance did high values offer real difficulty. This was the case of a patient with severe peripheral arteriosclerosis and diabetic neuritis (Case 20). The skin resistance of both feet was too high to read. Although my studies were not complete enough to permit me to be certain, I feel that this was an instance of sympathetic denervation which had occurred in the course of her disease, similar to cases which I have reported.<sup>3</sup> Even in this instance I was able to obtain confirmation of the efficacy of the sympathetic injection by studying the skin resistance of the legs, which was somewhat lower than that of the feet, with kaolin on the electrode, a procedure which lowers the readings. After injection the reading was 1,000,000 ohms on one leg and too high to read on the other. The patient was then warmed with blankets and hot water bottles and the same difference was found where one used the plain zinc electrode without kaolin. The sympathetic injection was not attended by rise in skin temperature, nor did any rise occur after a posterior tibial block was carried out as a check.

Case 18 illustrates another possible application of the method. This patient, who had severe peripheral arteriosclerosis and a recent popliteal thrombosis, was studied without skin resistance measurements. No rise in skin temperature followed paravertebral injection of procaine, and it was important to know whether a good sympathetic anesthesia had been obtained. Readings of skin resistance were then made and they confirmed the efficacy of the block. In this patient one could outline the entire extremity as having resistance too high to read, whereas the values on the contralateral limb were much lower. In Fig. 5 this contrast is shown. The area of high skin resistance is of the same extent as that found following first, second, and third lumbar ganglionectomy.<sup>1</sup> Injections of procaine had been made at the level of the first and second ganglia. In a number of other cases the area of sympathetic anesthesia could be outlined similarly, but not infrequently the readings on the thighs were too high to permit sharp outlining of the extent of anesthesia. Undoubtedly one could *do so* if he were to warm the patient sufficiently before the anesthesia had worn off and if the result should ever appear doubtful, I should follow this procedure.

The artificial fever of typhoid vaccination<sup>4</sup> is no longer employed as a test since more satisfactory methods have replaced it. The observation of temperature changes in cooled extremities when the body is warmed by a hot-air cabinet,<sup>5</sup> by wrapping in blankets and rubber sheet,<sup>6</sup> by electric pads, or by diathermy over the lumbosacral area<sup>7</sup> is a simple and helpful test. Similarly useful is the immersing of the other extremities in warm water.<sup>8</sup> I sometimes use such body-heating tests, especially when it is desirable to study vascular spasm both in upper and lower extremities at the same time. If good vasodilatation does not occur, however, I feel that it is necessary to check the matter by direct sympathetic injection or some other test. General anesthesia can be used to demonstrate the presence or absence of vasospasm<sup>9</sup> but is not ordinarily advisable unless anesthesia is necessary for some other purpose. Spinal anesthesia is similarly useful<sup>9, 10</sup> but must be restricted to good-risk patients who are hospitalized. It is particularly useful in those cases where it is important to study both lower extremities. A satisfactory test is the study of the temperature changes in the area innervated by a peripheral nerve after its effective block with procaine.<sup>11</sup> I frequently employ this test. It should not be used if there is an area of infection or gangrene adjoining the site at which the injection must be made. In many respects, however, the ideal test is the direct blocking of the sympathetic nerves with procaine.<sup>11, 12</sup> It has the advantage over all the other methods in that it permits one to study the effect upon pain of direct interruption of the sympathetic nerves, and I feel that it should always be employed when pain is present. Once complete sympathetic anesthesia is present one can study, in addition to the element of vasospasm and the vascular capacity for dilatation, the effect upon resting pains of all sorts, cutaneous hyperesthesia and tenderness, and intermittent claudication.

In general, one can judge very well by these preliminary studies what operative interruption of the sympathetics to a limb will accomplish. It has been my experience that the principles laid down by Morton and Scott<sup>13</sup> are fundamentally correct: Namely, the nearer the temperature of the previously cooled limb rises to the level to which a normal limb can be brought by the same test, the greater the improvement in circulation that can be obtained from sympathectomy. Where the operative results are not those anticipated from the preoperative studies, the variation is always toward a greater improvement than was anticipated. In recent years there has been a tendency to try the operation in some selected cases which formerly would have been considered unsuitable. Some patients in whom the preoperative sympathetic injection had brought about little or no rise in skin temperature have been sympathectomized with surprisingly good results, although commonly such patients have shown little improvement. One wonders whether in many of these cases

## DISCUSSION

Diminished peripheral arterial circulation may be due to occlusion of vessels, to vasospasm, or to a combination of the two. The determination of the category in which each case belongs and the degree of vasospasm present is not only helpful in sorting out the peripheral vascular diseases but is essential to their rational treatment. There is no way of restoring blood flow through obliterated arteries, but there are effective means of releasing vascular spasm. There are a number of useful tests for

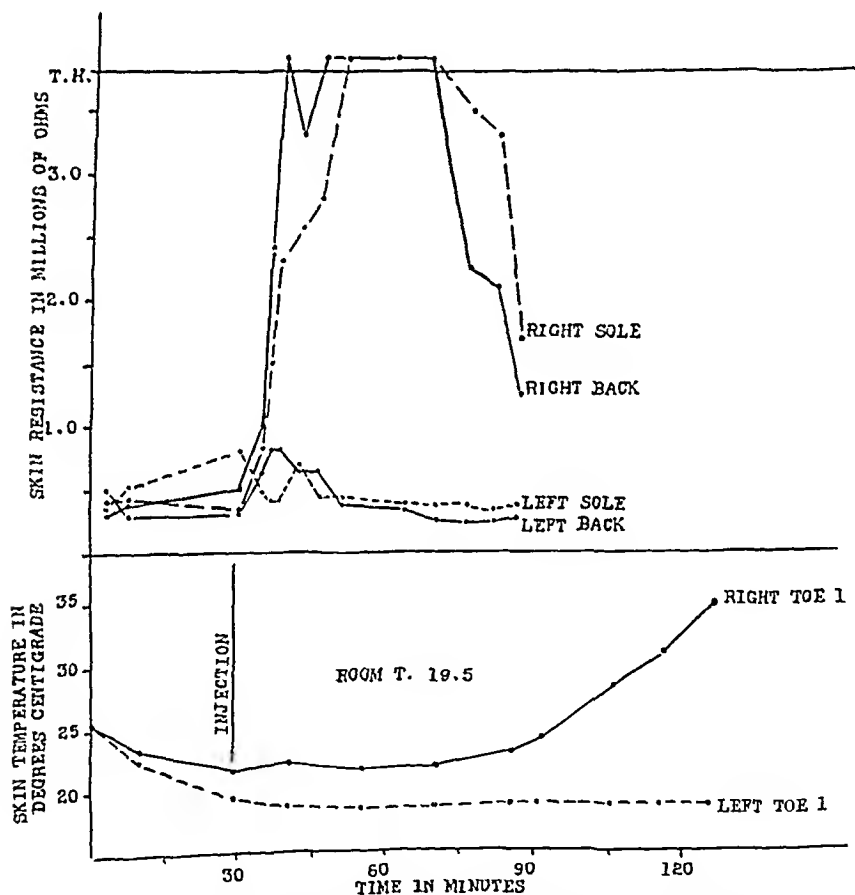


FIG. 6.—Showing prompt rise in skin resistance and delayed rise in skin temperature following right lumbar sympathetic block in Case 9 Buerger's disease

inhibiting sympathetic vasoconstrictor impulses, depending either upon release of vascular tone in some indirect manner or upon interruption of sympathetic impulses by anesthesia. The effect is usually noted by observation of changes in skin temperature. These observations may be supplemented by digital plethysmography, oscillometry, or plethysmographic blood flow studies.

## SUMMARY

The use of skin resistance studies in determining the accuracy of sympathetic injections is described, and the value of this procedure is discussed.

The author wishes to express to Dr. C. P. Richter, Mrs. B. G. Woodruff, and Miss M. Ascherfeld his appreciation of their cooperation in the skin resistance studies.

## REFERENCES

1. Richter, C. P., and Woodruff, B. G.: Changes Produced by Sympathectomy in the Electrical Resistance of the Skin, *SURGERY* 10: 957-970, 1941.
2. Levine, M.: Measurement of Electrical Skin Resistance, *Arch. Neurol. & Psychiat.* 29: 828-842, 1933.
3. Shumacker, H. B., Jr.: Sympathetic Denervation of the Feet and Legs Occurring Spontaneously or as a Result of Disease, A Preliminary Report, *Bull. Johns Hopkins Hosp.* In press.
4. Brown, G. E.: The Treatment of Peripheral Vascular Disturbances of the Extremities, *J. A. M. A.* 87: 379-383, 1926.
5. Lewis, T., and Pickering, G. W.: Vasodilatation in the Limb in Response to the Warming of the Body With Evidence for Sympathetic Vasodilator Nerves in Man, *Heart* 16: 33-51, 1931.
6. Coller, F. A., and Maddock, W. G.: The Differentiation of Spastic From Organic Peripheral Vascular Occlusion by the Skin Temperature Response to High Environmental Temperature, *Ann. Surg.* 96: 719-732, 1932.
7. de Takats, G.: The Differentiation of Organic and Spastic Vascular Occlusions, *Ann. Surg.* 94: 321-326, 1931.
8. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearm in Warm Water, *J. Clin. Investigation* 11: 1019-1036, 1932.
9. Morton, J. J., and Scott, W. J. M.: The Measurement of Sympathetic Vasoconstrictor Activity in the Lower Extremities, *J. Clin. Investigation* 9: 235-246, 1931.
10. Bull, S., and Lawrence, L. B.: Changes in Temperature of the Lower Extremities Following the Induction of Spinal Anesthesia, *Proc. Soc. Exper. Biol. & Med.* 27: 728, 1930.
11. White, J. C.: Diagnostic Blocking of the Sensory and Sympathetic Nerves. A Method of Estimating the Results Which Can Be Obtained by Their Permanent Interruption, *Am. J. Surg.* 9: 264-277, 1930.
12. White, J. C.: Diagnostic Blocking of Sympathetic Nerves to Extremities With Procaine, *J. A. M. A.* 94: 1381-1388, 1930.
13. Morton, J. J., and Scott, W. J. M.: The Quantitative Determination of Vasoconstrictor Spasm as a Basis for Therapy in Peripheral Arterial Diseases, *Ann. Surg.* 96: 754-766, 1932.
14. Ochsner, A., and DeBakey, M.: Thrombophlebitis; Role of Vasospasm in Production of Clinical Manifestations, *J. A. M. A.* 114: 117-124, 1940.
15. Homans, J.: Minor Causalgia Following Injuries and Wounds, *Ann. Surg.* 113: 932-939, 1941.
16. Gage, M., and Ochsner, A.: The Prevention of Ischemic Gangrene Following Surgical Operations Upon the Major Peripheral Arteries by Chemical Section of the Cervico-Dorsal and Lumbar Sympathetics, *Ann. Surg.* 112: 938-957, 1940.
17. White, J. C.: Technique of Paravertebral Alcohol Injection. Methods and Safeguards in Its Use in the Treatment of Angina Pectoris, *Surg., Gynec. & Obst.* 71: 334-343, 1940.



the inconsistency may be due to a poor sympathetic procaine injection. The use of skin resistance studies during the preliminary sympathetic block should help to answer this very important question.

I do not think that skin resistance studies will be necessary as a practical measure in all sympathetic injections. Certainly in studying upper extremities one rarely needs this additional aid, as the efficacy of the block is ordinarily evident from the Horner's syndrome and from the rise in skin temperature in the hand. It will be particularly helpful in lumbar sympathetic injections and especially in those cases in which it appears likely that the circulatory deficiency is largely due to obliterative disease. I think, also, that such studies should be carried out for investigative purposes in a very large number of cases of sympathetic injections. From such a study one might be able to evaluate better the preoperative studies and the postoperative results in regard to improvement in circulation, since one would know with certainty whether the sympathetic injection had given good anesthesia. It would help to elucidate such problems as the delayed response which was discussed in connection with Case 9. It is not at all unlikely that other questions might also be answered.

In addition to the sympathetic injections done in order to evaluate vascular capacity or pain and the aid which might be anticipated from sympathetomy, such injections are helpful in treating certain disorders and are essential in localizing the needles before introducing alcohol where a more permanent chemical sympathetic interruption is desired. Excellent results are being obtained from single or repeated injections of the sympathetic nerves in acute thrombophlebitis,<sup>14</sup> traumatic reflex edema, causalgia,<sup>15</sup> frostbite, and other vascular disorders. Procaine and alcohol injections are very helpful in assuring maximal vasodilatation before operative attack upon certain vascular lesions such as peripheral arterial emboli and aneurysms.<sup>16</sup> Alcohol block of the upper dorsal sympathetics is proving very useful in relieving pain in angina pectoris.<sup>17</sup> In many of these instances it is not essential that the affected extremity be cooled to the point of stabilization of skin temperature before injection, and sometimes such cooling is harmful, but without such exposure of the limb to cold there is always some chance for error in interpreting skin temperature changes as indicative of sympathetic anesthesia. Furthermore, one often desires to carry out such procedures in operating or treatment rooms which cannot be adequately cooled for the usual skin temperature studies. In such cases I believe study of the cutaneous resistance will give prompt and accurate information as to the efficacy of the sympathetic injection. Of course, the warmer the patient is at the time of the injection the more clear-cut will be the difference in cutaneous resistance on the injected and uninjected sides.

*Examination*—Height, 171.7 cm, weight, 79.6 kg, temperature, 37° C, pulse, 106; respirations, 20; blood pressure systolic 126, diastolic 80. The patient was well developed and nourished. He was cooperative, but excited, and obviously acutely ill. His skin was clear, his eyes markedly prominent with lid lag, pupils reacted normally, and fundi were clear. The mucous membranes of the nose, pharynx, and mouth were clear. There was bilateral, soft, nontender enlargement of the thyroid, which moved upward on swallowing. A bruit was present over the thyroid and there were visible forceful pulsations over both carotid vessels. His heart was rapid, regular, with normal sounds. He had pitting edema of both ankles. Hemoglobin was 13.5 Gm.; leucocyte count, 5,000, urine, negative, Wassermann reaction, negative, nonprotein nitrogen of the blood, 34 mg. per cent; basal metabolic rate +36.

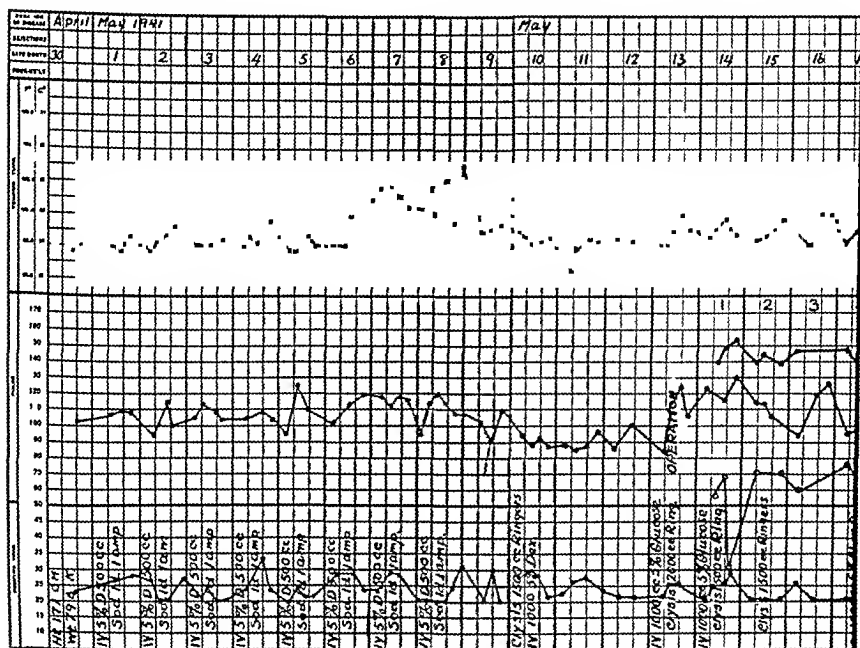


Fig 1—Shows febrile response to iodine becoming marked on the sixth day and extending through the eighth day. Immediate return to essentially normal temperature at withdrawal on the ninth day.

The patient was given 1 cc Lugol's solution orally three times daily, supplemented by 1 cc sodium iodide with 500 cc of 5 per cent glucose intravenously. At night he was given 0.1 Gm phenobarbital. He was on a high caloric diet, and had complete bed rest in a single room.

After five days of comfort, he complained of sore throat with coryza and conjunctivitis the following day. Shortly after there was profuse sweating, increase in restlessness, and apprehension. His temperature increased with each four hour period to 38.8° C during the second day of symptoms. Within twenty four hours however, his condition was alarming, with exacerbation of the symptoms already present augmented by diffuse itching, a macular rash on most of the body, and fever of 39.6° C.

The similarity of the rash to that of chronic iodine poisoning suggested the nature of the disturbance. All iodine solutions were immediately canceled. Rest was ob-

# ACUTE IODISM DURING THE TREATMENT OF TOXIC GOITER

PLIMPTON GUPTILL, M.D., ROCHESTER, N. Y.

(From the Department of Surgery, Strong Memorial Hospital, the University of Rochester)

**I**T IS widely accepted by surgeons that iodine for the treatment of toxic goiter is entirely harmless. This belief prevails regardless of the numerous instances, some serious, which occur during treatment in medical clinics.

Barker and Wood<sup>1</sup> first specifically studied 400 cases for unfavorable febrile reaction following oral iodine medication in toxic goiter. In this series there were 7 cases with unquestionable symptoms during the first four to ten days of use. At first appeared redness of the mucous membrane of the throat and nose, with conjunctivitis, temperature elevation, spiking in type, from 100° to 104° F., followed by sweating, itching, and macular rash of most of the body. However, with complete withdrawal of the iodine, symptoms rapidly disappear, except for minor febrile reaction for one to three weeks.

On the other hand, one patient developing iodism on the third day of administration of 3 c.c. of compound solution became markedly worse when the dosage was doubled. There was spread of the rash, desquamation, and hemorrhage into the palate.<sup>2</sup> Later complete withdrawal of iodine, and the institution of vigorous supportive measures failed to alter his course which terminated on the twenty-first day.

Necropsy showed "the skin covered with macular-papular desquamating rash." The thyroid was "enlarged, firm, dry, with many gray-white opacities." The lungs were "congested, with patches of lobular pneumonia. The lymph glands, spleen, liver were enlarged, and microscopically showed miliary inflammatory perivascular lesions" with areas of central necrosis.

Previous to the present illness, five of these seven patients had taken iodine without untoward symptoms, and subsequently, after an interval of months, again tolerated it with benefit.

L. L. D., 40-year-old male, presented himself April 30, 1941, because of nervousness. He had been well until four weeks before, when he had a severe upper respiratory cold, followed by extreme weakness. Shortly after he was jittery and his hands shook, he had profuse sweating, polydipsia, and anorexia. He was irritable, apprehensive, unable to work or concentrate. He lost ten pounds in weight, and for two weeks he had dyspnea, and swelling of the ankles.

At 19 years of age he had a double goiter treated successfully by oral iodine, otherwise he had always seemed well. He enjoyed his work, had good friends, and was happy at home.

Presented at the meeting of the Society of University Surgeons, Cincinnati, Ohio, Feb. 12-14, 1942.

were many small, closely packed acini containing only slight amounts of vacuolated colloid. They were lined by hyperplastic columnar epithelium that was redundant into the lumen. Many groups of small lymphocytes were scattered about.

At home his condition rapidly improved with gain in appetite and weight. After one week, however, he developed quite a marked inflammatory reaction in the left side of the draining wound of the neck, accompanied by pharyngitis. These conditions responded readily to treatment.

The sinus remained even after he was apparently well, and at infrequent intervals extruded spontaneously a silk ligature. At the end of three months, however, he was at his work six days a week, with normal vigor and enthusiasm for this and his private life. A moderate degree of exophthalmos persisted.

There are three types of unfavorable reaction of the individual from contact with iodine. With prolonged use of small amounts a macular-papular dermatitis develops which progresses to bulbous and ulcerative lesions if continued. Again certain persons have an intrinsic, marked cutaneous sensitivity resulting in diffuse erythema and swelling if iodine comes in contact with the normal skin. Barker and Wood observed one patient with cutaneous reaction who also had had a febrile manifestation from oral administration, but at a later date was free from both. One patient has been observed whose arm became red and swollen throughout from application of iodine for vein puncture. Lastly, those persons who have what appears to be true allergy to iodine. There is early and violent reaction manifested by mounting fever, irritation of all free mucous surfaces, dermatitis, and nervous irritability. Symptoms disappear rapidly on cessation of iodine, but under forced continuance may become serious or fatal.

In all eight cases reviewed, barbiturate of some form was used concurrent with iodine. However, this would not seem to have a direct bearing for phenobarbital was continued one week following the relief from iodine in this case.

#### CONCLUSIONS

1. Certain patients with toxic goiter are sensitive to oral iodine.
2. Symptoms of iodism occur early and progress if the drug is continued.
3. The continued use of iodine where there has been a febrile response is dangerous.
4. The basal metabolic rate is affected normally by iodine in persons showing a febrile response.
5. Operation is possible after relief of iodism.
6. Seven cases of iodism in toxic goiter were found in literature and one added.

#### REFERENCES

1. Barker, W. H., and Wood, W. B., Jr.: J. A. M. A. 114: 1029, 1940.
2. Moore, G. E.: The Modern Treatment of Syphilis, Springfield, Ill, 1933, Charles C Thomas, Publisher.

tained by morphine, 0.010 Gm. every four hours, and 2,000 c.c. Ringer's solution was given subcutaneously. Within eight hours of cessation of iodine, the patient was free of itch, fever had fallen from 39.6° to 37.5° C., and pulse dropped from 110 to 90.

Fig. 1 illustrates the rising temperature on the sixth, seventh, and eighth days of hospitalization concurrent with the appearance and exacerbation of symptoms. There was a sharp, crisislike drop at midnight of the eighth day. A basal rate taken on the seventh day was 420.

During the next four days the patient was given daily 1,000 c.c. of 5 per cent glucose intravenously, with 1,000 to 2,000 c.c. Ringer's solution subcutaneously, and sufficient morphine to obtain rest.

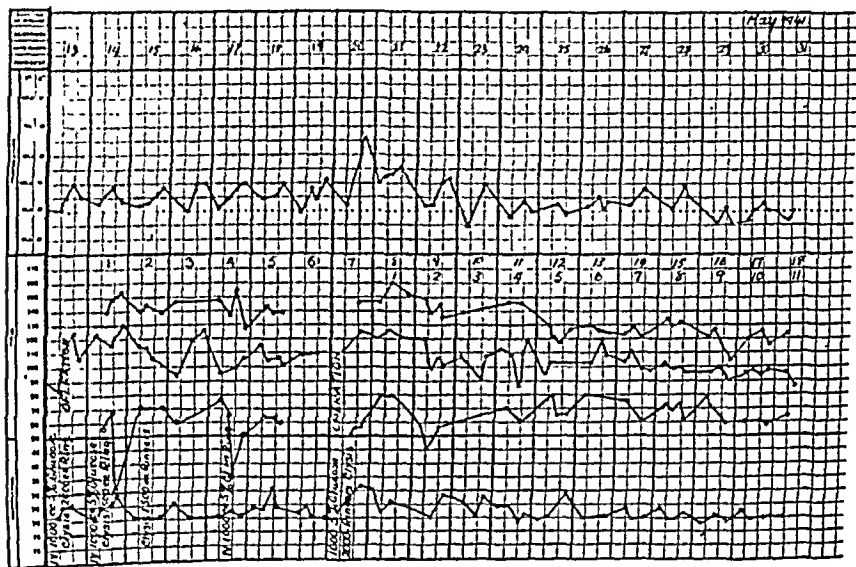


Fig. 2.—Shows postoperative course with a continued minor febrile reaction for two weeks.

On the thirteenth day of hospital care a right hemithyroidectomy was performed without difficulty or reaction, using avertin—gas-oxygen anesthesia. There was, however, a daily afternoon febrile reaction to 38° C. and difficulty in swallowing due to sore throat. The intravenous glucose also was continued, augmented by sufficient Ringer's solution to make the parenteral fluids 3,000 c.c. daily. Seven days later the left lobe was removed with moderate reaction but no evidence of postoperative storm. It had been noted at the second operation that healing was less advanced on the right side than expected. There was considerable serum without fibrin and the skin flaps were edematous. Five days later considerable serum escaped spontaneously from the left angle of the wound. *Streptococcus hemolyticus* and *Staphylococcus aureus* were cultured from this sinus. There was, however, little local inflammatory reaction and no change in his general condition which continued to improve. He was discharged eleven days after the second operation.

Examination of the removed thyroid showed diffuse symmetrical enlargement, each lobe measuring 7 × 5 × 3 cm. The texture was regular and the cut surface homogeneous. The right lobe weighed 50 Gm., the left 40 Gm. Microscopically there

Resection of the horizontal ramus of the jaw likewise causes no serious functional derangement. When the mandible is removed from the angle, or slightly above it, to the midline, there is a moderate inward sag of the soft tissues, which causes some facial asymmetry. This is accentuated by the projection of the cut end of the mandible near the symphysis. It is greater in those instances where the submaxillary gland and lymph nodes must be removed with the bone. Opening of the mouth is not restricted, but there is a shift of the jaw toward the lost side. As it is usually not practicable to wear a denture, mastication is not normal. Nutrition, however, can be satisfactorily maintained even for those engaged in rather heavy manual labor. Swallowing is not affected. Speech is at first blurred due to loss of teeth, loss of sensation, loss of some control of the lower lip on the resected side, and disturbance of the anterior muscular attachments of the tongue. This improves rapidly and in a few months is nearly normal. In these individuals the final speech is usually about that of an edentulous person.

Unlike resection of the ascending and horizontal rami, removal of the anterior, midline projection of the mandible results in marked functional disturbance. If the bone be removed from canine to canine there is a shrinking inward of the remaining halves of the mandible. This destroys the normal occlusion of the teeth, reduces the space in which the tongue can function, and produces noticeable deformity due to loss of support of the soft tissues of the chin. I believe that in order to preserve satisfactory function symphysis, losses of the mandible should be repaired by bone graft. If possible, this should be done at the original operation. However, this is rarely feasible, as in most instances the oral cavity is connected with the wound. In these instances it is best to maintain the horizontal rami on either side in normal relations by interdental fixation and as soon as soft tissue healing permits, insert a bone graft.

If a considerable amount of mucosa is removed with the jaw in any of these areas severe functional disturbance may occur. This is due to the inevitable contractures that develop as the wound heals. In ascending ramus resections with excision of mucosa near the angle, inability to open the mouth is liable to be the end result. After wide excisions of mucous membrane covering the horizontal ramus, the tongue is liable to be drawn forward as contracture occurs, until it protrudes from the mouth. This happens when the excision is forward. If the mucous membrane excision is lateral to the tongue and extends up onto the cheek it may be drawn downward and laterally. Closed bite seriously interferes with nutrition, since a more or less liquid diet is all that is possible. Contractures displacing the tongue affect both speech and swallowing.

#### INDICATIONS FOR RESECTION

Reference to resection of the lower jaw means the removal of a complete segment so that there is no bony continuity remaining. In a num-

## FUNCTION OF THE LOWER JAW FOLLOWING PARTIAL RESECTION

FORREST YOUNG, M.D., ROCHESTER, N. Y.

*(From the Department of Surgery, Plastic and Reconstructive Division, University of Rochester, School of Medicine and Dentistry)*

### FUNCTION OF THE LOWER JAW

THE lower jaw has multiple functions. These may be divided into support and movement.

The mandible is a hoop-shaped bone anatomically divided into three areas: the ascending rami, the horizontal rami, and the region of the symphysis. It acts as a point of attachment for a number of muscles, most of which are concerned with moving the jaw, but a certain number act from the mandible as a fixed point in moving the tongue.

Movement of the lower jaw is quite complex and takes place in the temporomandibular joints which are combination hinge, ball and socket, and gliding mechanisms. The construction of these joints is such that the lower jaw can open and close, glide forward and backward, and swing from side to side.

As a stationary bone the mandible supports the musculature of the face, maintains a space within which the tongue can function, and with the attached teeth is the structure on which the lips and tongue move in speech and deglutition.

### DISTURBANCES IN FUNCTION FOLLOWING PARTIAL LOSS OF THE MANDIBLE

It would seem from the nature of the functions which the mandible performs, that significant losses would seriously disturb function. It has been my experience that this is not necessarily so. Rather large segments of the mandible can be removed without seriously inconveniencing or disfiguring the patient. The loss of function which results depends upon the area of jaw removed and whether or not mouth lining must be sacrificed.

The ascending ramus on one side can be removed with almost no disturbance in function and scarcely noticeable disturbance in facial contour. Such a resection can extend forward to the premolar region of the horizontal ramus without further change in movements of the jaw or sacrifice of its supportive role. In such instances speech is unaffected, chewing is practically normal, and swallowing is undisturbed. There is at times a complaint of soreness in the remaining temporomandibular joint, probably due to strain. The excursion of the jaw is not restricted, but on wide opening there will be a shift of the jaw toward the resected side; this may be no more than the width of an incisor tooth.

## OPERATIVE METHODS WHICH PREVENT FUNCTIONAL DISTURBANCE

If possible, the resection should be done intraorally and without sacrifice of mucosa. This can be done in adamantinoma and benign tumors of small size.

In most instances where resection is indicated, it is also necessary to remove soft tissue rather widely. This is best done through external incisions. The majority of these lesions are in the horizontal ramus, and in those instances where a chance of cure seems present and it is



Fig. B—1, Neck flap; 2, cheek turned laterally, 3, mucous membrane of the cheek. The growth has been skirted by an incision through the mucous membrane of the cheek and along the lateral border of the tongue.

obvious that a large amount of mouth lining must be sacrificed, plans should be made to restore the lost lining at the time of resection. This is done by developing a flap on the neck prior to excision, or by a free skin graft inserted on a form (Figs. A and D). The approach which I have found most convenient is as follows: The lower lip is split in the midline and this incision carried downward to about the level of the hyoid; from here it turns at a right angle and runs toward the angle of the jaw. The mucosa of the cheek is incised from angle to midline of the lower lip, leaving a wide margin of mucosa and attached soft parts around the growth. Thus a flap of half the lower lip and the cheek is turned laterally allowing complete access to the jaw and mouth. The dissection starts in the neck in order to remove the suprahyoid triangle



ber of benign conditions affecting the mandible, excision of local areas of the bone is necessary. In these lesions a rim of bone can be left to maintain the arch. If one temporarily immobilizes the jaw, a rim of cortex inferiorly, no more than one-fourth of an inch thick, will suffice. In such cases, the mechanics of jaw opening and closure are not interfered with, although the alveolar ridge is, of course, deformed and special dentures are needed. The common conditions affecting the mandible, in which this local type of bone removal suffices, are dentigerous and dental root cysts, hemorrhagic cysts, giant cell tumor, osteoma, and perhaps small adamantinoma operated upon for the first time.

The indication for extensive resection of the lower jaw is usually the invasion of the bone by the direct extension of carcinoma arising in the

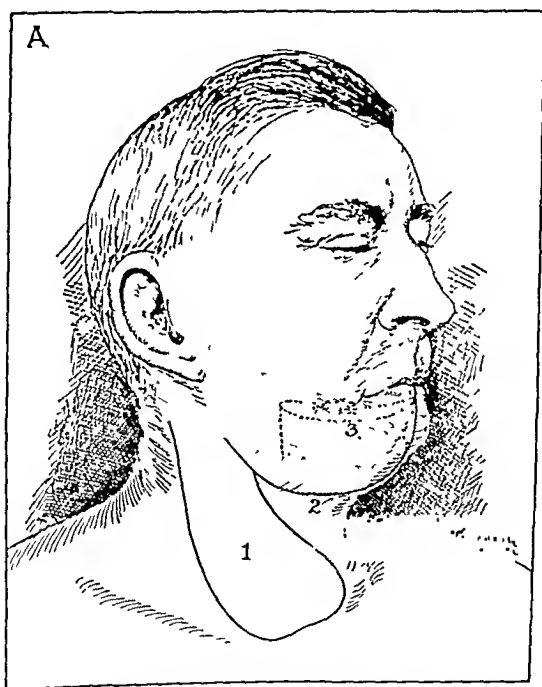


Fig. A.—Diagram of incisions used in excising a cancer of the alveolar ridge invading the mandible. 1, Flap previously delayed on neck; 2, incision through midline of lip and extending to angle of jaw. The flap so made is turned externally and allows complete access to the horizontal ramus and the suprahyoid lymph glands. 3, Area of mandible to be removed.

mucous membrane, or the occurrence of primary malignancy in the bone itself. Infection of the jaw bone is rarely an indication for resection. Osteomyelitis of the mandible is best treated by maintaining the normal arch by whatever mechanical means necessary, draining soft tissue abscesses, and sequestrectomy after sufficient involucrum has formed to maintain the arch. In chronic fibrous nonpurulent osteitis, resection is at times advisable.

showed a moderate erosion of the alveolar ridge. A biopsy was obtained and diagnosed as epidermoid carcinoma.

*Treatment.*—Because of invasion of the bone, surgical removal was decided upon rather than radiation. In order to resect widely enough to afford a chance of cure, it was thought that it would be necessary to excise a rather wide area of mucosa.

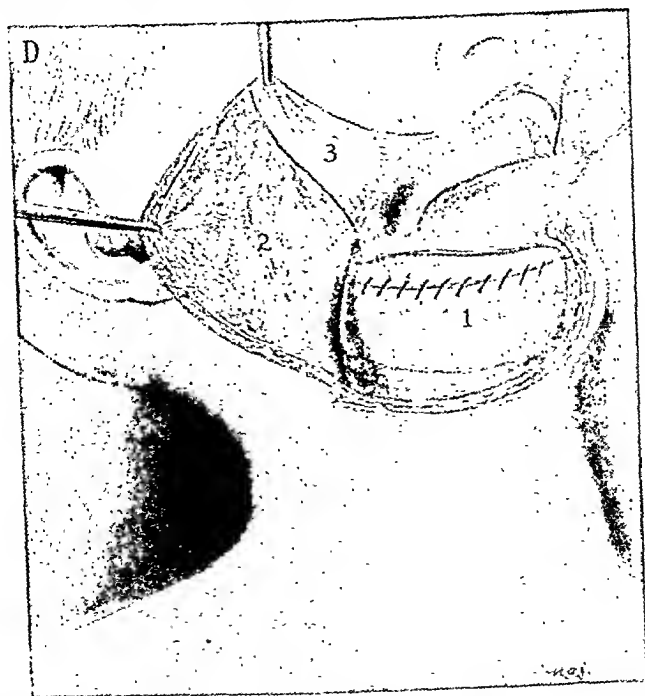


Fig. D.—An alternative method in which a wax form (1) with a Thiersch graft wrapped around it is used to replace the excised mucosa. The flap (2) is reflected back over this to its original location. The graft resurfaces the raw areas on the flap and joins onto the area of mucous membrane (3) which has been left.



Fig. 1.—Case 1. a, X-ray showing erosion of the alveolar ridge, right mandible, due to extension of squamous cell carcinoma of the mucosa; b, specimen removed at operation. The ulceration and surrounding mucosa can be seen. The mass includes the horizontal ramus of the jaw, the suprahyoid lymph glands, the submaxillary gland, and adjacent soft tissue. c, Functional result four and one-half years after resection. Right cheek lined with skin flap from neck.

of lymph glands en masse with the affected jaw. The jaw is sawed across near the midline and the mucosa incised along the tongue laterally. When the bone has been freed back to the angle, or further if necessary, it is cut across and the growth with the lymph gland area removed in one mass.

If a neck flap has been elevated previously this is now turned upward and used to reline the cheek and area from which the bone has been removed. If a free graft is used this is wrapped around a dental compound model and inserted into the cavity. The flap of cheek and lip is reflected back into position and sutured.



Fig C—The involved jaw has been removed with the suprahyoid lymph glands attached 1, Neck flap, 2, cheek turned laterally. The neck flap has been turned upward, rotated, and its edges sutured to the mucous membrane (3) of the cheek and to the mucous membrane along the tongue laterally, this neck skin (4) now becomes the mouth lining

#### CASE 1—W. E (S M H, No 126020)

*History*—A 63 year old white farmer was referred to the hospital by his dentist on April 6, 1937, because of a sore on the lower jaw. He stated that in January, 1936, over a year prior to entry, the gum of the right lower jaw became so sore that he had to stop wearing a denture which he had worn for over thirteen years. About a month prior to entry he had consulted his dentist because of increasing pain.

*Examination*—The positive findings were limited to the mouth which was endodontulous. In about the first molar region of the right lower jaw, there was an eroded, rough, raw area which was surrounded by a slightly raised, firm border. The erosion seemed to extend into the jaw bone. An x ray of the right mandible (Fig 1)

third molar to the canine region, the suprahyoid glands, and a wide margin of mucous membrane of the cheek and mouth floor was removed in a block. The flap from the neck was then used to repair the mouth lining (Figs. A, B, and C).

This healed in place satisfactorily except for a minor slough at its tip. Four weeks later the pedicle of the flap was cut and the granulating area on the neck, skin grafted.

*Results.*—He has been seen at frequent intervals to date, roughly four years after resection. There has been no recurrence. In spite of loss of most of the horizontal mandibular ramus on the right side there is no marked deformity. He speaks intelligibly. He cannot wear a lower denture but has gained weight, which is good evidence that he is able to eat fairly satisfactorily.

CASE 2.—R. M. (S. M. H., No. 57747).

*History.*—A 49-year-old male, white, engineer, first entered the clinic in February, 1932. About one year before he had noticed a small, hard, nontender nodule on the external surface of the midportion of the right mandible. This gradually grew larger. In December, 1931, it suddenly became greatly swollen, painful and tender, and a large amount of blood-tinged pus discharged spontaneously from about the second molar. He consulted a dentist, who extracted two right lower molar teeth.

*Examination.*—The positive findings were confined to the mouth and jaw. There were many teeth missing and the remainder were carious snags. There was a hard, round, nodular mass, about  $2\frac{1}{2}$  by  $1\frac{1}{2}$  inches in size connected with the midportion of the right horizontal ramus of the mandible. X-rays showed a large cystic area in the right horizontal ramus which extended from the second molar region forward to the right lateral incisor. A biopsy was characteristic of adamantinoma. On March 5, 1932, an intraoral local excision of the tumor was done. About one year later a recurrence was locally removed. He was not seen until four years later. He had had during this time a slowly progressive enlargement of the right jaw. I saw him for the first time in June, 1937. He then had a very large tumor involving almost the entire horizontal ramus of the right lower jaw. X-rays (Fig. 2b) showed cystic areas from the angle of the jaw almost to the symphysis. I advised resection.

*Treatment.*—The tumor was exposed through an external incision after placing a tape around the external carotid. The entire mass was removed from a little to the left of the symphysis to well past the angle, about one inch of the ascending ramus being removed. The mucous membrane in the mouth was left intact except for a small longitudinal strip over the midportion of the tumor, and could be closed by suture.

*Results.*—This man's case has been followed closely. He was last seen on May 8, 1941, and has had no recurrence. There is moderate sinking in of the right side of the face. The jaw shifts slightly to the right on wide opening (Fig. 2d). He does not wear a lower denture, but is able to do hard physical labor and has maintained his weight satisfactorily. Speech is normal except for the lisp associated with toothlessness.

CASE 3.—V. W. (S. M. H., No. 107153).

*History.*—I first saw this 12-year-old schoolgirl in September, 1935. About nine months prior to this she began to have a painful swelling of the left lower jaw. This had gradually become so constantly painful that she was continually taking salicylates for relief. She was unable to chew because of pain and had lost about eight pounds during the three months prior to entry. This swelling seemed to be intermittent in character.

The plan was to first elevate a flap on the neck so that tissue would be ready to repair the lining loss at time of resection.

On April 15, a flap was partially elevated and delayed on the right side of the neck. Two weeks later the flap was again elevated under local anesthesia and delayed. In two more weeks the flap appeared to have good circulation and resection and repair were carried out accordingly. This was done in the following manner: The lower lip was split in the midline and the incision continued to the level



Fig 2—Case 2. Resection of large recurrent adamantinoma, right horizontal ramus of mandible, through external incision. Only small amount of mucosa sacrificed which did not warrant replacement. *a*, Size of tumor, *b*, x-ray of excised specimen which shows destruction of mandible and extent of jaw removed. *c*, appearance four years after excision of right side of lower jaw, *d*, function of jaw four years postoperative.

of the thyroid cartilage; it then turned at right angles, to the right, and ended at the right angle of the jaw. Thus, a flap made up of the right side of the face could be reflected, and a large block of tissue containing the mandible from the

third molar to the canine region, the suprathyoid glands, and a wide margin of mucous membrane of the cheek and mouth floor was removed in a block. The flap from the neck was then used to repair the mouth lining (Figs A, B, and C).

This healed in place satisfactorily except for a minor slough at its tip. Four weeks later the pedicle of the flap was cut and the granulating area on the neck, skin grafted.

*Results.*—He has been seen at frequent intervals to date, roughly four years after resection. There has been no recurrence. In spite of loss of most of the horizontal mandibular ramus on the right side there is no marked deformity. He speaks intelligibly. He cannot wear a lower denture but has gained weight, which is good evidence that he is able to eat fairly satisfactorily.

CASE 2.—R. M. (S. M. H., No. 57747).

*History.*—A 49 year-old male, white, engineer, first entered the clinic in February, 1932. About one year before he had noticed a small, hard, nontender nodule on the external surface of the midportion of the right mandible. This gradually grew larger. In December, 1931, it suddenly became greatly swollen, painful and tender, and a large amount of blood tinged pus discharged spontaneously from about the second molar. He consulted a dentist, who extracted two right lower molar teeth.

*Examination.*—The positive findings were confined to the mouth and jaw. There were many teeth missing and the remainder were carious snags. There was a hard, round, nodular mass, about  $2\frac{1}{2}$  by  $1\frac{1}{2}$  inches in size connected with the midportion of the right horizontal ramus of the mandible. X rays showed a large cystic area in the right horizontal ramus which extended from the second molar region forward to the right lateral incisor. A biopsy was characteristic of adamantinoma. On March 5, 1932, an intraoral local excision of the tumor was done. About one year later a recurrence was locally removed. He was not seen until four years later. He had had during this time a slowly progressive enlargement of the right jaw. I saw him for the first time in June, 1937. He then had a very large tumor involving almost the entire horizontal ramus of the right lower jaw. X-rays (Fig. 2b) showed cystic areas from the angle of the jaw almost to the symphysis. I advised resection.

*Treatment.*—The tumor was exposed through an external incision after placing a tape around the external carotid. The entire mass was removed from a little to the left of the symphysis to well past the angle, about one inch of the ascending ramus being removed. The mucous membrane in the mouth was left intact except for a small longitudinal strip over the midportion of the tumor, and could be closed by suture.

*Results.*—This man's case has been followed closely. He was last seen on May 8, 1941, and has had no recurrence. There is moderate sinking in of the right side of the face. The jaw shifts slightly to the right on wide opening (Fig. 2d). He does not wear a lower denture, but is able to do hard physical labor and has maintained his weight satisfactorily. Speech is normal except for the lip associated with toothlessness.

CASE 3.—V. W. (S. M. H., No. 167157).

*History.*—I first saw this 12 year old schoolgirl in September, 1935. About nine months prior to this she began to have a painful swelling of the left lower jaw. This had gradually become so constantly painful that she was continually taking salicylates for relief. She was unable to chew because of pain and had lost about eight pounds during the three months prior to entry. This swelling seemed to be intermittent in character.

*Examination.*—There was no fever or any other constitutional signs of infection. There was a diffuse, firm enlargement of the left horizontal ramus from above the angle to about the first bicuspid. This was tender. The soft tissues over the bone did not appear thickened (Fig. 3a). The teeth were in excellent condition. The lymph glands in the left upper neck were enlarged, firm, and tender. There was no leucocytosis, and the Wassermann was negative. X-ray of the lower jaw showed diffuse increase in width and thickness, with spotty areas of decreased density (Fig. 3c). It was suspected that the disease was a low grade infection of some nature



Fig. 3.—Case 2. a, Enlargement of left side of face due to chronic fibrous osteomyelitis of mandible; b and c, specimen and x-ray of specimen removed. This left side of the jaw from the condyle to a little past the mental foramen is diffusely expanded. The x-ray shows multiple areas of decreased density. d, Appearance two years after operation. The jaw was removed subperiosteally and there has been a partial regrowth of the bone. e, There is a moderate shift to the shortened side on opening.

but a definite diagnosis could not be made. During December, 1935, the body of the mandible was explored through an external incision. The periosteum was thickened, the bone was greatly enlarged and its surface roughened. In several areas there were cortical perforations. By enlarging these it was found that the bone was spongy and soft. No pus was found. A culture was taken which proved negative and bone which was removed was diagnosed as chronic fibrous osteomyelitis.

The child was then seen at frequent intervals during 1936. In October of that year it became evident that she was progressively getting worse. The jaw had slowly enlarged, opening of the mouth becoming limited, and she was in almost constant pain. She was taking salicylates in large doses. X-rays showed progressive increase in the spotty areas in the bone and an increase in size. It was decided to resect the involved bone.

*Treatment.*—In November, 1936, the bicuspid and molar teeth were extracted and the sockets healed without trouble. About six weeks later, after the sockets were thoroughly healed, resection was done through an external incision. The left temporomandibular joint was disarticulated and the bone cut across just medial to the mental foramen (Fig. 3b). This resection was accomplished subperiosteally without entering the mouth. The right side of the jaw which remained was held in correct occlusion by interdental wiring. She gradually regenerated a small horizontal ramus and an ascending ramus up to about the coronoid notch. About a year after resection she began to complain of pain in the chin region and this area became swollen. X-rays showed an extension of the same process into the right side of the mandible as far as the right first molar. It was thought that removal of this involved bone would be necessary, and the remaining teeth on the right side were extracted. Following this there seemed to be some decrease in pain and swelling, and resection of the right side was deferred.

*Results.*—She was seen frequently for about two years after the extractions. She had recurrence of swelling and pain but there was a gradual improvement in symptoms. In December, 1940, x-rays showed a complete disappearance of the mottled areas in the right mandible. The left mandible had regenerated except for the condyle and coronoid process. There was a moderate sunken appearance of the left side of the face and pronounced shift of the jaw to the left on complete opening (Fig. 3 d and e). It was decided that a lower denture should be made. This is in process.

CASE 4.—W. W. (S. M. H., No. 125015).

*History.*—This 42-year-old white hotel clerk entered the clinic in February, 1937. He complained of pain in the left lower jaw. He began having trouble with the jaw about eight years before. At that time he had an impacted wisdom tooth and a small cyst removed from the lower jaw on the left. About four years later a growth developed in the same region and was removed. He then had no difficulty until about one week prior to my first seeing him. At this time he complained of pain and a sensation of the jaw being broken.

*Examination.*—At that time there was no visible or palpable swelling, but an x-ray of the left ascending ramus of the mandible showed a large cystic area replacing the ascending ramus (Fig. 4a). Other than an old poliomyelitic atrophy of the left lower leg, the remainder of the examination was negative.

*Treatment.*—The angle and ascending ramus of the left mandible were exposed through an external incision. There was a large cyst in the ascending ramus. There was no bone on the medial side of this tumor and only a thin eggshell-like bony wall externally. This cavity contained only a small amount of tumor tissue, but a large amount of brownish, moderately viscous fluid. The condyle did not seem to be greatly involved, but had no bony connection with the remaining jaw, conse-



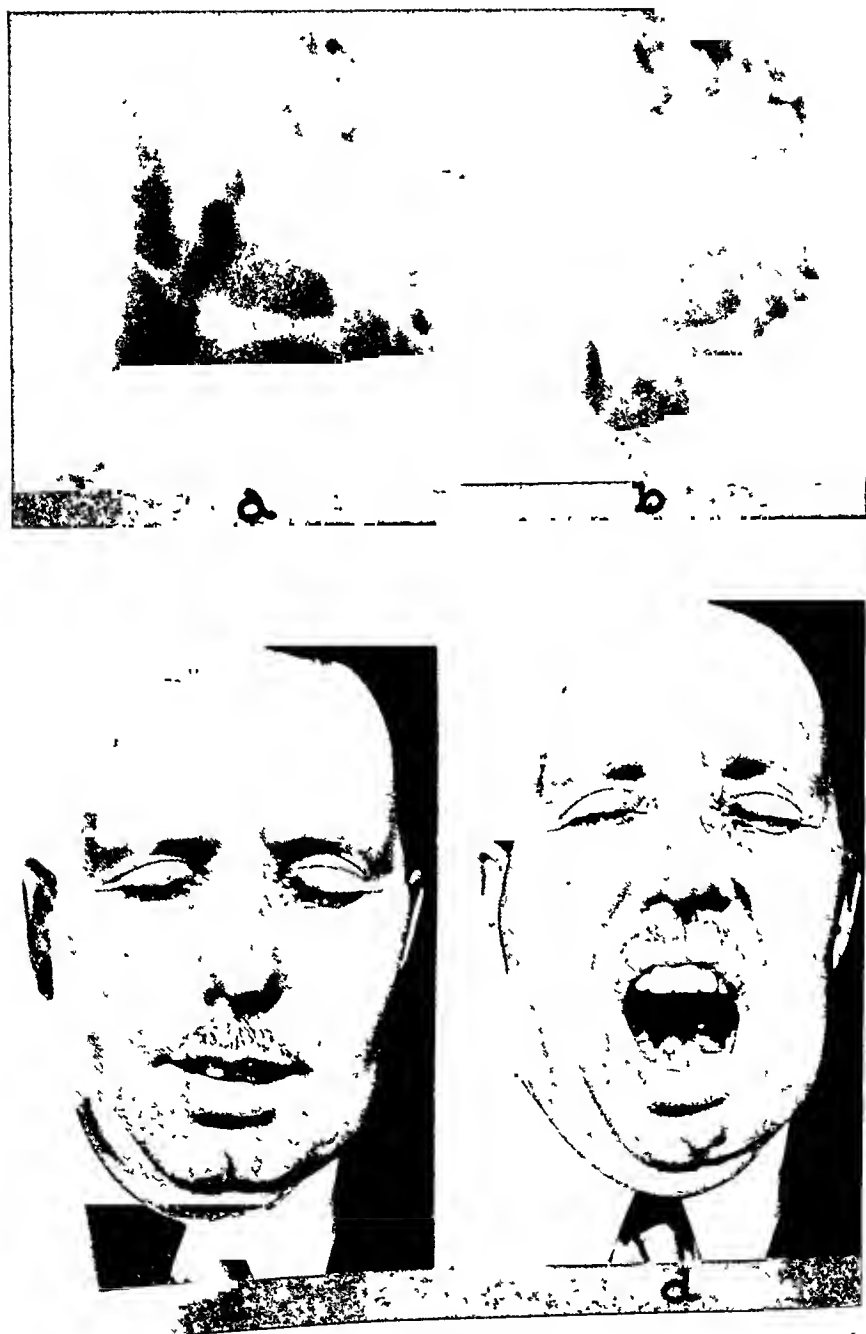


FIG 4—Case 4. Recurrent adamantinoma of ascending ramus, left jaw. Excised through external approach without entering mouth. *a*, X-ray showing large cystic area in ascending ramus; *b*, postoperative x-ray showing absence of ascending ramus; *c*, appearance four years after excision and shortly after removal of soft tissue recurrence; *d*, almost no disturbance in function. The only abnormality is a slight shift of the jaw toward left on wide opening.

quently, it and the coronoid process were completely removed. All suspicious bone fragments and soft tissue were removed, leaving a jaw which had no bone from the angle of the horizontal ramus upward (Fig. 4b). The tumor tissue removed was characteristic adamantinoma.

*Results.*—He recovered promptly and without difficulty. He was seen for a few months after operation and had no particular complaints. About four years later, in March, 1941, he reappeared with a large swelling in the parotid region on the left. This had come to his attention for the first time about two months before. He had no particular pain and the jaw function had not been disturbed. He was again operated upon and a large cyst with small intramural tumors was removed; this, too, was adamantinoma. This operation was rather difficult and the patient had a stormy immediate postoperative course, due to shock from blood loss. He recovered and is at present back at his former job as a hotel clerk. He has good function of the jaw and has had for the past four years, without an ascending ramus. He can chew anything, has no pain, and the only abnormality on examination is a light shift of the jaw to the left on wide opening (Fig. 4d).

CASE 5.—C. K. (S. M. H., No. 154820).

*History.*—This 79-year-old retired Irishman complained of pain about the angle of the left lower jaw and a small ulceration of the gum in this region. About a year before he first came to me in September, 1939, he had begun to have intermittent soreness of the gums and would occasionally omit wearing his lower denture for about a day or so. About six months later he noticed a tiny ulceration in the left lower gum posteriorly. This had never bled, and had increased only slightly in size. For the past two months he had not worn his lower denture because of discomfort.

*Examination.*—He was a well-preserved, mentally alert old man. The mouth was edentulous. There was a small ulceration about 1 cm. in diameter on the left lower alveolar ridge in about the location of the third molar. There was a firm, hard enlargement of the angle of the mandible which seemed to extend upward in the ascending ramus. X-rays showed an area of bone destruction, multilocular in character, near the angle of the left jaw; this seemed to extend upward toward the condyle. A small piece of tissue was secured from deep in the ulcer for microscopic examination. There was considerable discussion about the diagnosis of this biopsy, but most of the pathologists thought it was a carcinoma of the cylindroma type.

I thought that the x-ray and the clinical course indicated an adamantinoma and I advised local excision on that basis.

*Treatment.*—At operation an incision was made intraorally around the ulcer, and a cystic area in the mandible at the left angle was exposed. It was found that this contained a firm cellular tumor not characteristic of adamantinoma. A frozen section was made and it was evident that the tumor was a carcinoma of glandular type. It was also found that this tumor extended upward as far as one could reach into the ascending ramus. It was therefore decided to resect the involved portion of the jaw. The joint on the left was disarticulated, the body of the mandible cut across in the bicuspid region and this portion removed (Fig. 5a). This was completed through the original intraoral approach. Sections of the specimen were examined and diagnosed as carcinoma of the cylindroma type replacing bone marrow.

*Results.*—He recovered promptly and was able to be on a soft diet on the twelfth postoperative day. Since then he had been seen frequently. He complains of numbness of the left lower lip and a feeling of tightness on the left side on opening. He at times complains of some soreness in the right temporomandibular joint. There

is no noticeable deformity (Fig. 5b). There is a slight shift of the jaw to the left on opening. He has been able to maintain his weight satisfactorily and as yet, one and one-half years later, there is no evident recurrence. He does not wear a lower denture.

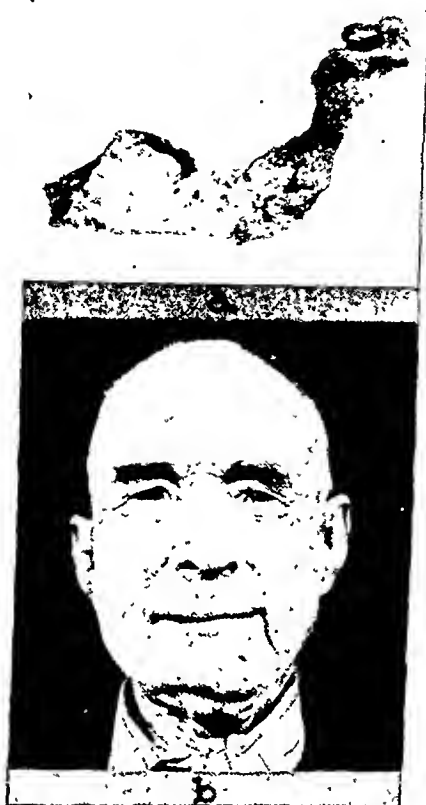


Fig. 5.—Case 5. Intraoral resection of the left mandible from condyle to bicuspid region for cylindroma. *a*, Specimen removed. The mandible has been partially destroyed by the growth. *b*, Appearance two years after resection. Unfortunately a photograph showing function was not obtained, but the patient does have satisfactory opening with only moderate shift to the left.

CASE 6.—I. K. (S. M. H., No. 153369).

*History.*—This 34-year-old housewife was sent to us for an opinion and treatment in May, 1939. About one and one half years before she had noticed a slight swelling of the right side of her chin, and soreness of the lower incisor teeth. She consulted a dentist who x-rayed the jaw and told her that she had a tumor of the bone. In December, 1937, a surgeon removed the tumor. Following this there were four recurrences and excisions at about sixty-day intervals. Following the fifth excision the growth again grew rather rapidly. Pathologic examination of the previously removed tissue was reported to us as osteogenic sarcoma.

*Examination.*—When we saw her some one and one-half years after onset, and with her sixth recurrence, there was an obvious firm mass involving the anterior projection of the mandible. It involved most of the body on the right, and extended into the horizontal ramus on the left to about the canine region. In the central portion of the tumor there was infiltration of the skin, but no ulceration.

An x-ray of the jaw showed the typical shooting-star radiations of bone characteristic of osteogenic sarcoma (Fig. 6a).

*Treatment.*—Because of the repeated recurrences, the nature of the growth, and the proximity to skin it was decided to resect the bone and soft tissue of the chin in one block, recognizing that repair of soft tissues and bone would be necessary. In May, 1939, this was done preserving only the hypoglossal nerves and the vermilion border of the lower lip. Following this the soft tissues were reconstructed in four steps (Fig. 6c). Following the last operation, at which flaps from the neck had been turned up in place to form mouth lining and skin of the lower face, the patient about two hours after operation suddenly became apneic and died. It was thought that death was due to obstruction of the airway. Post-mortem examination showed no demonstrable metastases.

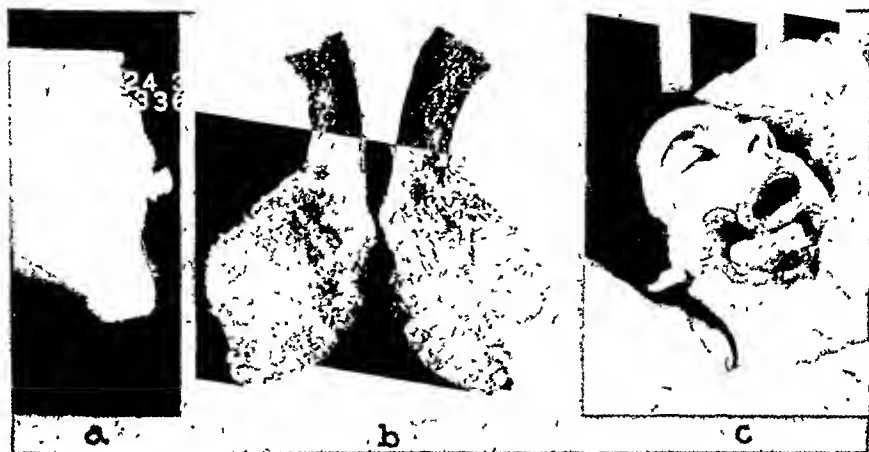


Fig. 6.—Case 6. Resection of mandible from angle to angle with involved soft tissues because of osteogenic sarcoma. *a*, Typical x-ray appearance of osteogenic sarcoma of mandible; *b*, excised specimen. The major portion of the growth involves the symphysis. *c*, Appearance of patient two weeks after resection. In this type of resection repair is, of course, imperative. In this instance, lining and covering of the cheeks and skin were reconstructed from three separate neck flaps, and following this a bone graft had been contemplated. The patient died of respiratory difficulty a few hours after the fourth step. A post-mortem showed no demonstrable metastases. In this type of resection, replacement of bone is necessary for both function and appearance.

#### CASE 7.—R. B. (S. M. H., No. 157559).

*History.*—This housewife, 65 years of age, began to have pain in her right jaw and ear about fifteen months before I first saw her in September, 1939. She went to three different dentists and had her lower denture altered, but without relief. Her family doctor, whom she then consulted, advised her to have an x-ray of the jaw. This showed an impacted wisdom tooth which was extracted in January, 1939. The tooth socket healed slowly, and about March, 1939, a swelling of the jaw developed. An x ray was again taken and she was told that she had a tumor of the jaw. She was then given deep x-ray therapy to the right lower jaw for a number of months. Her pain, however, persisted. The swelling she believes may have increased slightly. She then consulted me.

*Examination.*—She was a very thin woman who appeared older than 65. The right side of the jaw was noticeably swollen (Fig. 7a), this swelling extending down into the submaxillary and submental region. The mouth was edentulous. A little to the midline there was a puckered, burrowing ulcer about 2 cm. in diameter on the alveolar ridge. The base of this ulcer was friable and bled easily. An x-ray of the jaw showed that the bone in the bicuspid region was almost completely severed by the ulceration (Fig. 7b). A biopsy of the ulcer base showed squamous cell carcinoma.

*Treatment.*—This lesion should have been considered inoperable because of the wide extension into soft parts, but in an attempt to relieve her of pain, resection was done in October, 1939. It was obvious that a large amount of the mouth lining would have to be removed, but because of the small chance of cure it was decided to disregard repair of this. The resection was done in block fashion, from a little anterior to the angle of the jaw on the right to slightly past the midline on the left. The submaxillary and submental lymph glands were removed with the section of jaw, as well as the mouth floor on the right and anteriorly (Fig. 7c). The



Fig. 7.—Case 7. Advanced carcinoma of right alveolar ridge. *a*, The growth has extended into soft tissues causing a noticeable enlargement of the right side of the face; *b*, the x-ray confirms the extent of the growth. It has eroded through almost the full width of the bone. *c*, The specimen includes the horizontal ramus and lymph gland area; *d*, protrusion of the tongue and difficulty in swallowing were the main complaints postoperatively. This was due, I believe, to a wide removal of mucosa without replacement, and not to recurrence which was present one and one-half years after resection when this photograph was obtained.

growth was found to invade the undersurface of the tongue, and the right hypoglossal nerve had to be sacrificed along with a portion of the undersurface of the tongue. This left a large area on the right and under the tongue denuded of mucous membrane. This was closed under considerable tension, and in so doing

the tongue was drawn quite far forward. The immediate course was quite stormy, characterized by difficulty in breathing as well as in the ingestion of food.

*Results.*—She recovered slowly and for about a year was free of pain. However, she had been quite uncomfortable during this entire period due to a gradual protrusion of the tongue, which was accompanied by what appeared to be a lymphedema of the right half of the tongue. About fifteen months after operation she again began to complain of pain, and there was an obvious recurrence in the soft tissues of the neck on the right side. She was given deep x ray therapy with moderate relief. She is still living about one and one-half years after operation, but in pain. At no time has function of her jaw been satisfactory. This, I attribute, not to the bone loss, but to failure to provide for the large loss of lining. This allowed the tongue to become adherent in a contracted, forward position, which interferes greatly with swallowing and speech.

CASE 8.—F. H. (S. M. H., No. 173353).

*History.*—A 60 year old white, male, bartender was referred to me on June 21, 1941, because of a recurrent squamous cell carcinoma in the floor of the mouth on the right side.

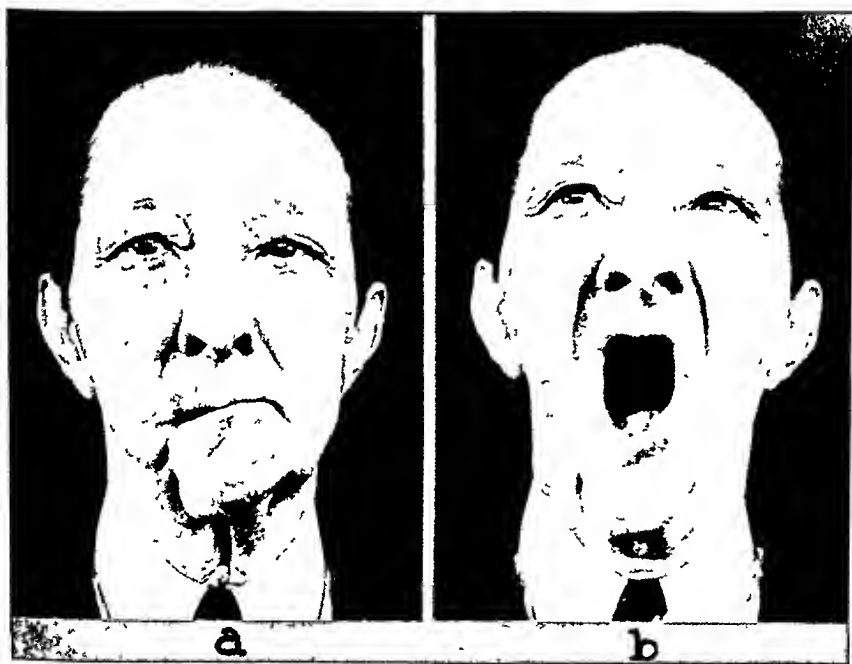


Fig 8—Case 8 Carcinoma of right alveolar ridge rapidly recurrent following x-ray therapy and local surgery a, Appearance after resection of right horizontal ramus and replacement of mucosa by a free skin graft on a stent, b, function is not greatly impaired

Fourteen months before, he had a lower right molar tooth extracted because of pain. Six weeks later another molar tooth was extracted from the same region. About one month later he noticed a growth along the alveolar margin where the teeth had been extracted. This gradually increased in size but caused him no pain and there was no bleeding. He consulted numerous physicians and dentists during this period, but evidently the diagnosis was not suspected. In January, 1941, a positive diagnosis was made of squamous cell carcinoma by biopsy. In addition, a

four plus Wassermann reaction was obtained. The lesion in the mouth was treated between Jan. 8 and Feb. 5, 1941, with 6000 r. x-ray with an intraoral cone in divided doses of 300 r. The usual local reaction followed this therapy with disappearance of the tumor.

On March 19, six weeks after completion of the course of x-ray therapy, there was an obvious recurrence along the alveolar ridge. An x-ray of the right mandible at this time showed no invasion of the bone. On April 3, 1941, a right suprahyoid neck dissection was done and the intraoral recurrence removed locally. Microscopic examination of this tissue showed typical squamous cell carcinoma of oral mucosa and questionable lymph gland involvement.

On May 20, 1941, about six weeks after the local excision, a recurrence was evident. He was referred to me at that time.

*Examination.*—The general examination was negative except for a four plus Wassermann. Local examination showed the neck incision well healed. There was a definite swelling of the soft tissues over the midportion of the right horizontal ramus. There was friable, vascular tumor about the neck of the first bicuspid tooth. The alveolar ridge was bare and necrotic from this tooth to the angle of the jaw, and in the adjacent mucous membrane in the region of the first molar there was a patch of tumor. It was evident that there was a recurrence of the growth extending into the soft tissues lateral to the jaw. A radical excision was advised.

*Treatment.*—On June 31, 1941, a block resection of the involved area was done. After extracting the left lateral and central lower incisors, the lip was split in the midline to the hyoid. A connecting incision from the angle of the jaw to the lower end of the vertical incision was made. This flap of tissue was reflected laterally leaving a wide margin of normal mucous membrane around the horizontal ramus (Figs. A and B). The jaw was cut across through the area of extraction, and through the ascending ramus about one inch above the angle of the jaw.

An incision was made in the mucous membrane along the tongue laterally and around the angle of the jaw to join the lateral incision. The mass of soft tissue and bone was lifted out in one piece. The flap was sutured back in place and the raw interior covered with a large, split, thick skin graft on a wax mold (Fig. D).

*Results.*—He had a rather difficult postoperative course. Due to difficulty in swallowing he lost about thirty pounds of excess weight. The graft took fairly well and he gradually gained strength and freedom of tongue action. In two months he returned to his old job as a bartender and is still performing his duties satisfactorily. He has now gone about eight months without recurrence.

He has free opening of the mouth, but is unable to wear either an upper or lower denture. In spite of this, his nutrition is good and he is able to work. The right side of the face is noticeably sunken and a prosthesis to hold the cheek out in normal position is to be constructed.

#### SUMMARY AND RESULTS

The mandible has functions of support and movement. These are intimately related to appearance, speech, chewing, and swallowing. The ascending or horizontal ramus of the lower jaw, or both, can be removed without too seriously impairing function. If the symphysis region is excised, great disturbance in function results unless the bone loss is repaired.

If a considerable amount of soft tissue and mucosa is removed with the resected bone, functional disability ensues. This can be prevented by repair of the mucosal loss without bone replacement.

# Editorial

---

## Traumatic Injuries to the Peripheral Vessels in Both Civil and Military Practice

THE incidence of injuries to the peripheral vascular tree will be greatly increased because of the large number of nations at war today. In peace time these injuries are usually treated by physicians trained in vascular surgery, whereas in time of war they are cared for largely by the general surgeon. For these reasons, it is absolutely necessary that all medical officers in the armed forces be thoroughly cognizant of the pathologic-physiologic conditions induced by arterial and arteriovenous injuries, as well as of the principles underlying the successful management of these cases. Proper treatment will reduce the loss of life and limb to a minimum, thus enabling a larger number of men to return to active or limited duty.

In modern warfare, high explosive and bullet injuries to the vascular tree in the extremities are liable to be excessive. These injuries range from simple contusion with segmental spasm to complete severance and destruction of the main peripheral vessels. Contusion of vessels is preceded by soft tissue bruises made by shell fragments or bullets passing through the tissues without primarily involving the vessels. The explosive force is transmitted to the vessel wall by continuity of tissue. This results in intramural bleeding with secondary luminal thrombosis or degenerative changes in the vessel wall which gradually give way to produce an aneurysm. In a number of cases there is not only intramural bleeding but rupture of the intima with rapid vascular occlusion by thrombosis. Therefore, a wide range of vascular lesions are produced by contusions, differing only in degree and extent, with a similar range in the incidence of permanent changes, that is, from segmental spasm or partial and complete thrombotic luminal occlusion to late aneurysmal formation.

Direct injuries result in partial or complete severance of the vessel wall, with or without complete segmental loss of the arterial wall and accompanying veins. The immediate effect of this type of injury depends upon whether the wound is semiclosed (puncture wound, bullet or fine shell fragment) or is widely lacerated or open. In the former, there is immediate bleeding into the perivascular tissue with hematoma formation. Bleeding is stopped by pressure of the hematoma upon the



vessel as well as segmental vasomotor spasm which contracts the vessel at the site of injury. After days or weeks the hematoma forms a pseudoarterial aneurysm. Therefore, every localized hematoma associated with a punctured wound should be considered a potential arterial aneurysm. Occasionally, this type of arterial injury continues to bleed into the tissue and muscular planes to produce irreversible shock resulting in death of the patient. I have seen three such cases.

In lacerated wounds with considerable segmental destruction or severance of the vessels, the patient may succumb from hemorrhage and shock (which is usually the case during battle), or shock may occur, lowering the blood pressure to such a degree that bleeding automatically stops. This may save the patient's life if local and systemic treatment can be instituted before shock becomes irreversible.

When the vein as well as the artery is injured, the peripheral and central blood streams are converted into a common pool. A hematoma forms and a firm tumor mass results. After days or weeks an arteriovenous aneurysm appears. This type of aneurysm has both local and systemic effects and differs from the pure traumatic arterial aneurysm in that the latter has no cardiac effects. The cardiac condition resulting from an arteriovenous aneurysm is at times sufficient to produce cardiac decompensation. This depends entirely upon the size of the vessels, the size of the arteriovenous opening, and the proximity to the heart. Therefore, in all traumatic injuries to the peripheral vessels, the occurrence of both pure arterial and arteriovenous aneurysms should be anticipated.

The peripheral vascular tree is controlled by the sympathetic nervous system which contains both vasomotor constrictor and dilator fibers. Stimulation of the system at any level along its peripheral course produces spasm of the vessels supplied, whereas destruction or blocking of the constrictor fibers results in vasodilatation of the vessels. This applies to both arteries and veins. Therefore, an injury to the peripheral vessels will result in segmental spasm. This may be sufficient to produce luminal obliteration which may persist long enough to produce thrombotic occlusion of the artery and all of its pathologic consequences. The point of injury of the vessel frequently acts as focus for initiating a spreading vasomotor spasm which involves not only the main peripheral arteries and veins but all of their branches as well. If spasm of the vessels continues for a long time, obliteration of the vasa vasorum occurs to prevent vessel wall nutrition and invoke internal changes resulting in thrombosis, ischemic gangrene, and loss of limb.

In order that proper treatment may be instituted, a thorough understanding of this pathologic physiology is not only essential but absolutely necessary. Five fundamental principles should be observed in the management of traumatic injuries of the peripheral vascular tree: absolute control of hemorrhage, treatment of shock, surgical correction of the injury, treatment of arterial and arteriovenous aneurysms,

and control of the sympathetic nerve supply to the peripheral vessels.

Hemorrhage can usually be controlled by a tourniquet or by local compression bandages. This will suffice until aseptic surgical procedures can be undertaken. Shock should be combatted by plasma infusions and blood transfusions. Plasma infusions can be given at any time or place because of the modern methods of processing, storing, and transporting plasma. Thus, plasma infusions are preferable to blood transfusions, because the use of plasma obviates the necessity of delay.

Surgical treatment of the injury should be performed under aseptic conditions. In puncture wounds with vascular injury, it is advisable to operate in the first few hours even if hemorrhage has not been controlled. If this is not possible, operation should be deferred until the hematoma has organized. The resulting arterial or arteriovenous aneurysm can be treated at a later date. From three to six months later is the optimal time.

Lacerated wounds with or without destruction of the vessels should be debrided, sulfanilamide sprinkled into the wound, and the vessels ligated. Arterial suture is a highly developed art which consumes time, and, as a rule, thrombosis occurs at the suture line. Therefore, in war, arterial continuity restored by suture is seldom indicated.

The late sequelae of arterial and arteriovenous traumatic injuries are arterial and arteriovenous aneurysms. These pathologic clinical entities should be treated according to the methods of Matas. The exception to this "postponement rule" is an acute arteriovenous aneurysm in which there is an extensive opening between the large caliber vessels, and in which cardiac dilatation is rapidly taking place. Here, simple ligation of the proximal vein will tide the patient over this distressing complication and the arteriovenous fistula can be repaired at a later date.

The fifth and, I believe, the most important factor is control of the pathologic function of the sympathetic nerve supply to the peripheral vessels. Maintenance of collateral circulation, segmental as well as diffuse vasomotor spasm of the peripheral arteries and their branches is controlled by preventing vasospastic impulses from reaching the main arteries and veins. This fundamental principle, if observed, restores adequate blood volume flow through the main arterial stem and its branches and thereby prevents ischemic gangrene.

When a patient has an injury in the peripheral vascular tree, the peripheral pulse should be thoroughly investigated. If it is absent, vasomotor spasm is present and is of major importance. Regardless of the type of vascular wound, blocking out the sympathetic ganglionated chain by chemical means (1 per cent novocain, or novocain and alcohol, 95 per cent) is urgently indicated. Sympathetic block should be repeated once or twice in the twenty-four hours and continued until arteriovenous spasm has been overcome and the tissues distal to the injury are adequately nourished. For the lower extremity, the first to

the fourth lumbar sympathetic ganglia should be blocked, and for the upper extremity the stellate ganglion should be injected. We have used this method in all traumatic injuries of the peripheral vessels as well as for aneurysms for the past twelve years without the occurrence of a single case of ischemic gangrene.

In recapitulation, in all traumatic injuries of the peripheral vessels, hemorrhage should be stopped by a tourniquet or compression bandages, shock prevented or overcome by plasma infusions and blood transfusions, injured vessels repaired or ligated, vasomotor spasm of the vessels prevented by sympathetic block, and arterial and arteriovenous aneurysms treated by the accepted methods of Matas.

—*Mims Gage, M.D.*  
New Orleans, La.

# Review of Recent Meetings

---

## THE SOCIETY OF UNIVERSITY SURGEONS

THE Fourth Annual Meeting of the Society of University Surgeons was held at the Cincinnati General Hospital and Children's Hospital, Feb. 12-14, 1942.

On the first day, Feb. 12, 1942, there was a general inspection of the Department of Surgery of the University of Cincinnati and presentation of interesting cases and problems under investigation by the local group.

During the sessions held on February 13 and 14 papers were presented by various members and these appear in this number of the journal. Papers presented and not published, or read by title include:

Franklin E. Walton (Washington University): Auxins in Relation to Certain Phases of Wound Healing.

Edward S. Stafford, and John Staige Davis (Johns Hopkins): Successful Construction of a Complete Extrathoracic Esophagus.

William F. Rienhoff (Johns Hopkins): A Clinical and Experimental Study on the Closure of the Primary Bronchus Following Total Pneumonectomy.

Alexander Brunschwig (Chicago): The Operative Treatment of Cystadenomas of the Pancreas.

the fourth lumbar sympathetic ganglia should be blocked, and for the upper extremity the stellate ganglion should be injected. We have used this method in all traumatic injuries of the peripheral vessels as well as for aneurysms for the past twelve years without the occurrence of a single case of ischemic gangrene.

In recapitulation, in all traumatic injuries of the peripheral vessels, hemorrhage should be stopped by a tourniquet or compression bandages, shock prevented or overcome by plasma infusions and blood transfusions, injured vessels repaired or ligated, vasomotor spasm of the vessels prevented by sympathetic block, and arterial and arteriovenous aneurysms treated by the accepted methods of Matas.

—*Mims Gage, M.D.*  
New Orleans, La.

book must be based on personal experience, for there are fewer than four dozen references to the literature. There are but nineteen illustrations. Although the book impresses one as being far more verbose than necessary in view of the contents, nevertheless there is much sound advice in it.

---

**An Introduction to Medical Science.** By William Boyd. Ed. 2. Pp. 358, with 124 illustrations. Philadelphia, 1941, Lea & Febiger. \$3.50.

This book is intended primarily for the nurse beginning her professional career. The first section of the book deals with the general principles of disease, the second with the diseased organs, and the third with some practical applications. The subject matter is written so completely and well that it is difficult to cite individual chapters for excellence. The only objection to this volume is that some of the illustrations are too diagrammatic (Figs. 42 and 76) to be clear. This book should have a wide popularity and should go through many future editions.

---

**The Blood Bank and the Technique and Therapeutics of Transfusion.** By R. A. Kilduffe and Michael DeBakey. Pp. 558, with 214 illustrations and one color plate. St. Louis, 1941, The C. V. Mosby Co. \$7.50.

The opportune and timely appearance of this book is striking. Indeed, the presentation of few subjects in medicine currently would be more propitiously received than the "various considerations and more recent developments in transfusion in a readily available compendious and expository source."

The book consists of sixteen chapters including history, rationale, indications and contraindications, military aspects of transfusion, special types of transfusion, technique of blood typing and compatibility tests, the nature, causes, detection and methods for the elimination of anomalous blood-typing reactions, the "Universal Donor" and the "Universal Recipient," the blood bank and its operation and changes occurring in stored blood, preparation and preservation of fresh and processed plasma, methods and technique of transfusion, and complications of transfusion. While it is admittedly "difficult to embrace within reasonable space limits all the various phases of blood transfusion," the authors have succeeded in their "endeavor . . . to present the subject in a comprehensive manner" and "to maintain the functions of expediency and practicability." Written in an eloquent, concise, and distinctly lucid style, the authors have combined the various laboratory and clinical aspects of the subject with explicit thoroughness. Following each chapter, there is an exhaustive list of references placed in alphabetical order. That the bibliography may be "considered sufficiently extensive, varied, representative, and inclusive not only to document the text but also to serve as a reference source for those interested in the respective phases of the subject" is clearly demonstrated by the fact that the chapter on Rationale, Indications, and Contraindications contains over nine hundred references. The value of these references is further enhanced by their actual inclusion in the text.

The profuse illustrations deserve special comment. Most of these consist of line drawings executed with such refreshing vigor and distinctive simplicity as to permit unusual ease of interpretation.

In view of the fact that transfusion has recently received its greatest impetus toward a wider application and is currently undergoing intensive investigation and development, this comprehensive, authoritative, and up-to-date consideration of the subject will undoubtedly meet a ready and cordial reception by clinicians as well as laboratory technicians.

## Book Reviews

---

**Accidental Injuries.** By Henry H. Kessler, M.D., Ph.D., F.A.C.S., Ed. 2. Pp. 803, with 202 illustrations. Philadelphia, 1941, Lea and Febiger Co. \$10.

This is a book of 803 pages with 202 illustrations and is concerned mainly with the physician's responsibility in the interpretation of the medicolegal aspects of workmen's compensation and public liability. The author has first presented a discussion of laws and rules followed by a surgical and medicolegal discussion of injuries in every part of the body. He has also discussed diseases and poisonings which may arise among workmen and be attributed to occupations. Numerous court decisions are presented in illustration of various injuries.

It is impossible to review in detail or even list the numerous subjects covered. This book is a very useful reference for the inexperienced or experienced practitioners who may be called to report upon or testify in workmen's compensation injuries and diseases and in public liability cases.

---

**Neuroanatomy.** By Fred A. Mettler, A.M., M.D., Ph.D., Professor of Anatomy, University of Georgia School of Medicine. Pp. 476 with 337 illustrations. St. Louis, 1941, The C. V. Mosby Co. \$7.50.

This text is written for the medical student with a view to preparing him for clinical medicine. Consequently, it provides a useful reference book for the physiologist, neurologist, and neurosurgeon. The first portion of the book deals with the topography and morphology of the central nervous system as seen with the naked eye. Throughout this section attention is continually drawn to those general anatomic relationships and concepts which form the basis for the manipulations of practical medicine.

The second part of the work, which is the microscopic section, concerns itself with the establishment of a sound and usable functional viewpoint. Special attention has been given to the matter of terminology. No new terms are employed at any place in the text without having been previously defined.

A carefully chosen list of references is included, with definite preference shown to articles in English and in readily accessible American journals. The book is beautifully illustrated with 337 photographs, diagrams, and drawings, a number of which are in color.

---

**Treatment of the Patient Past Fifty.** By Ernst P. Boas, M.D. Pp. 308, with 19 illustrations. Chicago, The Year Book Publishers, Inc. \$4.

In this small book of 308 pages, the author discusses at length the general philosophy of dealing with elderly patients, and constantly emphasizes the importance of consideration of the psychologic effects of the diseases, age changes, and advice to which this group is heir. There is fairly broad discussion of the management of diseases grouped in systems: cardiovascular, pulmonary, gastrointestinal, biliary, genitourinary, etc. The chief message in this book seems to be that the elderly patient requires much more constant medical attention than do younger patients, and that a great amount of thought should be given to the mental outlook. The

# INDEX TO VOLUME 11

## AUTHORS INDEX\*

In this index following the author's name, the title of the subject is given as it appeared in the Journal. Editorials are also included in the list and are indicated by (E).

### A

- ADAMS, W. E., STEINER, PAUL E., AND BLOCH, ROBERT G. Malignant adenoma of the lung, 503
- ADIE, GEORGE C., HUESTED, LESTER C., CHILDRESS, WILLIAM G., AND PEREZ, HORACIO E. Paravertebral thoracoplasty for the treatment of pulmonary tuberculosis, 788
- ALTEMEIER, WILLIAM A. The pathogenicity of the bacteria of appendicitis peritonitis, 374
- ARENS, ROBERT A. (See Kroll, Arens, Mesiro, Strauss, and Necheles), 810

### B

- BALKIN, SAMUEL G. (See Waldron and Balkin), 183
- BALL, ZELDA B. (See Visscher, Ball, Barnes, and Sivertsen), 48
- BARCHAM, IRVING S. (See Bodenheimer and Barcham), 710
- BARNES, RICHARD H. (See Visscher, Ball, Barnes, and Sivertsen), 48
- BELL, E. T. Exudative interstitial nephritis (pyelonephritis), 261
- BENEDEK, TIBOR. Fusospirochetal onychia and paronychia, 75
- BERGH, GEORGE S. The splinter mechanism of the common bile duct in human subjects, 299
- BERMAN, A. L., SNAPP, E., AND IVY, A. C. The effect of bile salts on recovery of liver function after release of common duct obstruction, 1
- BLALOCK, ALFRED. A comparison of the effects of the local application of heat and of cold in the prevention and treatment of experimental traumatic shock, 356
- (See Little, Harrison, and Blalock), 392
- BLOCH, ROBERT G. (See Adams, Steiner, and Bloch), 503
- BLODGETT, JAMES B. An evaluation of intestinal suction in intestinal obstruction, 739

- BOALS, ROBERT T. (See Chunn, Harkins, and Boals), 56
- BODENHEIMER, MILTON, AND BARCHAM, IRVING S. Skeletal manifestations of thyroid disease, 710
- BOWERS, RALPH F. The surgical treatment of carcinoma of the stomach in aged individuals, 869
- BOYS, FLOYD. The prophylaxis of peritoneal adhesions, 118
- BURTON, S. (See Medoff and Burton), 596
- BUTLER, M. F. (See Nadler and Butler), 732

### C

- CAMPBELL, DARRELL A. Some observations on the Quick hippuric acid test in hepatic function, 195
- CATTELL, RICHARD B., AND SUGARBAKER, EVERETT D. Recent advances in the surgical treatment of carcinoma of the colon and rectum, 644
- CHILDRESS, WILLIAM G. (See Adie, Huested, Childress, and Perez), 788
- CHUNN, C. FRANK, HARKINS, HENRY N., AND BOALS, ROBERT T. Experimental studies on alimentary azotemia. III. Site of blood absorption, 56
- COFFEY, ROBERT J. Unilateral hypertrophy of the masseter muscle, 815
- COLLINS, CONRAD G. (See Weed and Collins), 292
- COPPLAND, MURRAY M. Bone tumors with reference to their treatment, 456
- COPLAND, SIDNEY M. The scalenus anticus factor in congenital torticollis, 624
- COX, FRANK J. Review of the meeting of the American Academy of Orthopedic Surgeons, tenth annual convention, Atlantic City, N. J., Jan. 11-15, 1942, 832
- COZEN, L. N. Positioning in surgery of the extremities, 605

\*January, pp. 1-168, February, pp. 169-312, March, pp. 313-502, April, pp. 503-670, May, pp. 671-810, June, pp. 811-1001



**Surgical Clinics of North America.** A Symposium on Military Surgery written by a number of authors, December, 1941. Volume 21, No. 6. Pp. 333, with 389 illustrations. Philadelphia, W. B. Saunders Company.

This small volume affords a review of the current military practices in the Army and Navy of the United States. Well-known authors contribute articles on the fields of their interest. The book contains much useful information on subjects of very live concern to all surgeons and can be recommended for orientation of the surgeon in our present war effort.

---

**Thoracic Surgery.** By Charles W. Lester. Ed. 1. Pp. 141. London, Oxford University Press.

This little book attempts to present in true outline form the salient information needed by physician, surgeon, and student on anatomy, physiology, anesthesia, the various disease entities of the chest, and the surgical treatment thereof. There are no illustrations. This volume should be handy for purposes of reference by one encountering this type of case frequently, but it seems too cryptic and abridged to fulfill the needs of the student, and insufficiently detailed to satisfy the thoracic surgeon. Nevertheless, it is a convenient "refresher" to have on hand for the treatment of the occasional case.

# INDEX TO VOLUME 11

## AUTHORS INDEX\*

In this index following the author's name, the title of the subject is given as it appeared in the Journal. Editorials are also included in the list and are indicated by (E).

### A

- ADAMS, W. E., STEINER, PAUL E., AND BLOCH, ROBERT G. Malignant adenoma of the lung, 503
- ADIE, GEORGE C., HUESTED, LESTER C., CHILDRESS, WILLIAM G., AND PEREZ, HORACIO E. Paravertebral thoracoplasty for the treatment of pulmonary tuberculosis, 788
- ALTFNEIER, WILLIAM A. The pathogenicity of the bacteria of appendicitis peritonitis, 374
- ARENS, ROBERT A. (See Kroll, Arens, Mesiro, Strauss, and Necheles), 810

### B

- BAIKIN, SAMUEL G. (See Waldron and Balkin), 183
- BALL, ZFIDA B. (See Visscher, Ball, Barnes, and Sivertsen), 48
- BAPCHAM, IRVING S. (See Bodenheimer and Bapcham), 710
- BARNES, RICHARD H. (See Visscher, Ball, Barnes, and Sivertsen), 48
- BELL, E. T. Exudative interstitial nephritis (pyelonephritis), 261
- BENFIER, TIBOR. Fusospirochetal onchia and paronychia, 75
- BERGH, GEORGE S. The splinter mechanism of the common bile duct in human subjects, 299
- BREMAN, A. L., SNAPP, E., AND ILL, A. C. The effect of bile salts on recovery of liver function after release of common duct obstruction, 1
- BLACK, ALFRED. A comparison of the effects of the local application of heat and of cold in the prevention and treatment of experimental traumatic shock, 156
- (See Little, Harrison, and Black), 92
- BLOCH, ROBERT G. (See Adams, Steiner, and Bloch), 503
- BLANCHETT, JAMES B. An evaluation of intestinal suction in intestinal obstruction, 719

- BOAIS, ROBERT T. (See Chunn, Harkins, and Boais), 56
- BODENHEIMER, MILTON, AND BAPCHAM, IRVING S. Skeletal manifestations of thyroid disease, 710
- BOWERS, RALPH F. The surgical treatment of carcinoma of the stomach in aged individuals, 869
- BOYS, FLOYD. The prophylaxis of peritoneal adhesions, 118
- BURTON, S. (See Medoff and Burton), 596
- BUTLER, M. F. (See Nadler and Butler), 732

### C

- CAMPBELL, DARRELL A. Some observations on the Quick hippuric acid test in hepatic function, 195
- CATTELL, RICHARD B., AND SUGARBAKER, EVERETT D. Recent advances in the surgical treatment of carcinoma of the colon and rectum, 644
- CHILDRESS, WILLIAM G. (See Adie, Husted, Childress, and Perez), 788
- CHUNN, C. FRANK, HARKINS, HENRY N., AND BOAIS, ROBERT T. Experimental studies on alimentary azotemia. III. Site of blood absorption, 56
- COFFEY, ROBERT J. Unilateral hypertrophy of the masseter muscle, 815
- COLLINS, CONRAD G. (See Weed and Collins), 292
- COPLAND, MURRAY M. Bone tumors with reference to their treatment, 436
- COPLAND, SIDNEY M. The scissorial factor in congenital torticollis, 624
- COX, FRANK J. Review of the meeting of the American Academy of Orthopedic Surgeons, tenth annual convention, Atlantic City, N. J., Jan. 11-15, 1942, 832
- COZIN, L. N. Positioning in surgery of the extremities, 605

- CRAIG, WINCHELL MCK. (*See* Turner, Craig, and Kernohan), 81  
 CRUMPACKER, LEO K. (*See* Waugh, Herrell, and Crumpacker), 385

## D

- DEPREE, JAMES F. (*See* Metz, Householder, and DePree), 586  
 DOWDY, ANDREW H. (*See* Stabins and Dowdy), 898  
 DRASH, E. C., AND WOODWARD, FLETCHER D. The treatment of impenetrable esophageal strictures by a combined intraesophageal and extraesophageal approach, 886

## F

- FEDER, J. M. (*See* Wrenn and Feder), 456  
 FONG, E. E. (*See* McCorkle and Fong), 851  
 FREELAND, M. R. (*See* Theis and Freeland), 101  
 FRICKE, ROBERT E. (*See* Madding and Fricke), 45

## G

- GAGE, MIMS. Traumatic injuries to peripheral vessels in both civil and military practice, 983 (*E*)  
 GARCIA, MANUEL. (*See* Pearson and Garcia), 636  
 GERMAN, WILLIAM J. Surgical treatment of spasmodic facial tic, 912  
 GIBSON, JOHN G., II. (*See* Keeley and Gibson), 527  
 GRANTHAM, EVERETT G. (*See* Mayfield and Grantham), 589  
 GRAY, HOWARD K., AND SKINNER, IRA C. Hemorrhagic cysts of the lung: report of two cases in which marsupialization was done, 777  
 GUPTILL, PLIMPTON. Acute iodism during the treatment of toxic goiter, 962

## H

- HALL, HOWARD. (*See* Kremen, Hall, Koschmitzke, Stevens, and Wangenstein), 333  
 HARKEN, DWIGHT E. Congenital malformations of the rectum and anus, 422  
 HARKINS, HENRY N. (*See* Chunn, Harkins, and Boals), 56  
 —, AND SCHUG, RICHARD. The surgical management of varicose veins: importance of individualization in the choice of procedure, 402  
 HARRISON, CARRINGTON. (*See* Little, Harrison, and Blalock), 392

- HART, VERNON L. Impacted fracture of the hip, 472 (*E*)  
 —. Reduction of supracondylar fracture in children, 33

- HARVEY, H. D., MELENEY, F. L., AND RENNIE, J. W. R. Peritonitis. III. Studies in peritoneal protection with particular reference to action of sulfonamide drugs in experimental peritonitis, 244

- HARVEY, SAMUEL C. (*See* Taffel and Harvey), 841

- HEDIN, RAYMOND F. (*See* Kabat and Hedin), 766

- HERRELL, WALLACE E. (*See* Waugh, Herrell, and Crumpacker), 385

- HOLCOMBE, R. GORDON, JR. (*See* Storck and Holcombe), 703

- HOLMAN, CRANSTON W., AND MCSWAIN, BARTON. Transthoracic esophagogastronomy, 882

- HORSLEY, GUY W. (*See* Poer and Horsley), 653

- HORWITZ, THOMAS. The effect of sulfanilamide crystals, used topically, on the fate of transplanted bone, 690

- HOUSEHOLDER, RAYMOND. (*See* Metz, Householder, and DePree), 586

- HUESTED, LESTER C. (*See* Adie, Huested, Childress, and Perez), 788

- HYNDMAN, OLAN R. Treatment of major wounds of the skull. I. Cerebral fungus: treatment by skin grafting, 466

## I

- IVY, A. C. (*See* Berman, Snapp, and Ivy), 1

## K

- KABAT, HERMAN, AND HEDIN, RAYMOND F. A nervous factor in the etiology of shock in burns, 766

- KASINSKAS, WILLIAM. (*See* Rhoads and Kasinskas), 38

- KATZ, L. N. (*See* Megibow, Katz, and Steinitz), 19

- KAWAICHI, G. K. (*See* Tashiro, Pratt, Kobayashi, and Kawaichi), 671

- KEATING, F. RAYMOND, JR., POWER, MARSCHELLE H., AND PRIESTLEY, JAMES T. Postoperative cholorrhea, 198

- KEELEY, JOHN L., AND GIBSON, JOHN G., II. Experimental atelectasis in dogs, 527

- KERNOHAN, JAMES W. (*See* Turner, Craig, and Kernohan), 81

- KOBAYASHI, N. (*See* Tashiro, Pratt, Kobayashi, and Kawaichi), 671

- KOOISTRA, HENRY P. Pilonidal sinuses occurring over the higher spinal segments with report of a case involving the spinal cord, 63
- KOSCHNITZKE, HERMAN K. (See Kremen, Hall, Koschnitzke, Stevens, and Wangenstein), 333
- KOZOLL, DONALD D., AND NECHELES, H. A study of gastrointestinal motility in the dog following ileocolostomy and partial colonic resection, 360
- KREMEN, ARNOLD J., HALL, HOWARD, KOSCHNITZKE, HERMAN K., STEVENS, BEATRICE, AND WANGENSTEEN, OWEN H. Studies on the intravenous administration of whole bovine plasma and serum to man, 333
- KROLL, H., ARENS, ROBERT A., MESIROW, S., STRAUSS, S. F., AND NECHELES, H. Localization of bismuth in the kidney, 810

## L

- LITTLE, JAMES MAXWELL, HARRISON, CARRINGTON, AND BLALOCK, ALFRED. Chylothorax and chyloperitoneum, 392
- LONG, CARROLL H., AND OCHSNER, ALTON. Intravenous pentothal sodium anesthesia, 474
- LORD, JERE W., JR. (See Quinn, Lord, and Wade), 229
- (See Quinn, Lord, and Wade), 233

## M

- MADDING, GORDON F., AND FRICKE, ROBERT E. Secondary or postoperative parotitis, 45
- MARTIN, J. D., JR., AND ROBERTSON, ROY. Blood studies during anesthesia, 11
- MAYFIELD, FRANK H., AND GRANTHAM, EVERETT G. Spinal extradural cysts, 589
- MCCORKLE, H., AND FONG, E. E. The clinical significance of gas in the gall bladder, 851
- MCLAUGHLIN, CHARLES W., JR. The surgical treatment of large carbuncles in diabetic and nondiabetic individuals, 797
- MCSWAIN, BARTON. (See Holman and McSwain), 882
- MEDOFF, JOSEPH, AND BURTON, S. A case of shock and hyperpyrexia induced by intravenous glucose infusion, 596
- MEHROW, R. S., KATZ, L. N., AND STEINITZ, F. S. Dynamic changes in experimental pulmonary embolism, 19
- MELENEY, F. L. (See Harvey, Meloney, and Rennie), 244

- MESIROW, S. (See Kroll, Arens, Mesirow, Strauss, and Necheles), 810
- METZ, ARTHUR R., HOUSEHOLDER, RAYMOND, AND DEPREE, JAMES F. Obstruction of the stomach due to congenital double septum with cyst formation, 586

## N

- NADLER, SAMUEL B., AND BUTLER, M. F. The cephalin-cholesterol flocculation test in the jaundiced patient, 732
- NECHELES, H. (See Kozoll and Necheles), 360
- (See Kroll, Arens, Mesirow, Strauss, and Necheles), 810
- (See Schwartz, Reingold, and Necheles), 746
- , AND OLSON, WM. H. Experimental investigation of gastrointestinal secretions and motility following burns and their relation to ulcer, 751
- NESSA, CURTIS B. (See Paine and Nessa), 281

## O

- OCHSNER, ALTON. The use of refrigeration combined with vasodilatation to preserve vitality in a relatively ischemic extremity, 819 (E)
- (See Long and Ochsner), 474
- OLSON, WM. H. (See Necheles and Olson), 751

## P

- PAINE, JOHN R., AND NESSA, CURTIS B. Observations on the distribution and transport of gas in the gastrointestinal tract of infants and young children, 281
- PAPERMASTER, RALPH. (See Sperling, Weisman, and Papermaster), 600
- PARTIPILO, A. V., AND WILTRAKIS, G. A. Duodenal obstruction, 557
- PEARSE, HERMAN E. Whipple's disease, or intestinal lipodystrophy, 906
- PEARSON, BJARNE, AND GARCIA, MANUEL. Intestinal obstruction as a phase of carcinoma of the cervix, 636
- PEREZ, HORACIO E. (See Adie, Huested, Childress, and Perez), 788
- POER, D. HENRY, AND HORSLEY, GUY W. Review of the Southern Surgical Association Meeting, Dec. 9-11, 1941, Pinchurst, N. C., 653

- POOL, J LAWRENCE Myelosecopy in traspinal endoscopy, 169
- POPPE, J. K. The use of a cold air blast on precancerous skin lesions and hemangiomas, 460
- POWER, MARSCHELLE H (See Keating, Power, and Priestley), 198
- PRATT, O B (See Tashiro, Pratt, Kobayashi, and Kawauchi), 671
- PRISTLEY, JAMES T (See Keating, Power, and Priestley), 198

## Q

- QUINBY, WM C, AND SIMEONE, F. A Some observations on acute renal hypertension, 544
- QUINN, WILLIAM C, LORD, JLEE W, JR, AND WADE, LEO J. Gas gangrene of the abdominal wall, 233
- , —, AND — Welch bacillus infections arising from the stomach and duodenum, 229

## R

- RAY, BRONSON S, AND SIEWART, HAROLD J. Observations and surgical aspects of the carotid sinus reflex in man, 915
- REINGOLD, IRVING (See Schwartz, Reingold, and Necheles), 746
- RENNIE, J W R (See Harvey, Meloney, and Rennie), 244
- RHOADS, JONATHAN E, AND KASINSKAS, WILLIAM The influence of hypoproteinemia on the formation of callus in experimental fracture, 38
- RIVES, J D Splenectomy, 223
- ROBERTSON, ROY (See Martin and Robertson), 11
- ROGLIANO, ALBERT G. Two cases of rat bite fever, 632
- ROURKE, G MARGARET (See Stewart and Rourke), 939

## S

- SCHUG, RICHARD (See Harkins and Schug), 402
- SCHWARTZ, ARTHUR H, REINGOLD, IRVING, AND NECHFLES, H A study on the mechanism of action of prostigmine on intestinal motility in the human being and in the dog, 746
- SHUMACKER, HARRIS B, JR Hemangioma of the liver, 209
- The value of skin resistance studies in determining the accuracy of procaine injections of the sympathetic nerve, 949

- SIEGEL, SIGMUND A Recent surgical physiology of the pancreas, 821
- SIMEONE, F A. (See Qumby and Simeone), 544
- SIVERTSEN, IVAR (See Visscher, Ball, Barnes, and Sivertsen), 48
- SKINNER, IRA C (See Gray and Skinner), 777
- SNAPP, E (See Berman, Snapp, and Ivy), 1
- SPARKMAN, ROBERT S, AND WILLIAMS, WILLIAM H The employment of cotton suture material in the field, 698
- SPENCE, HARRY M Meeting of the Urological Section of the Southern Medical Association, St Louis, Mo, Nov. 12 & 13, 1941, 496
- SPEHLING, LOUIS, WEISMAN, SYDNEY, AND PAPERMASTER, RALPH The effect of intravenous theophylline with ethylene diamine (aminophylline) upon the rate and depth of respiration, 600
- STABINS, SAMUEL J, AND DOWDY, ANDREW H Carcinoma of the breast, 895
- STEINER, PAUL E (See Adams, Steiner, and Bloch), 503
- STEINITZ, F S (See Megibow, Katz, and Steinitz), 19
- STEVENS, BEATRICE (See Kremen, Hall, Koschmitzke, Stevens, and Wangenstein), 333
- STEWART, HAROLD J (See Ray and Stewart), 915
- STEWART, JOHN D, AND ROURKE, G MARGARET Vitamin A content of plasma and hepatic tissue biopsied at operation effects of preoperative therapy in obstructive jaundice, 939
- STORCK, AMBROSE H, AND HOLCOMBE, R GORDON, JR The use of estrogenic substances in the preoperative and postoperative treatment of hyperthyroidism, 703
- STRAUSS, S F (See Kroll, Aiens, Mesirov, Strauss, and Necheles), 810
- SUGARBAKER, EVERETT D (See Cittel and Sugarbaker), 641

## T

- TAFFEL, MAX, AND HARVEY, SAMUEL C. Ludwig's angina, 841
- TASHIRO, K, PRATT, O B, KOBAYASHI, N, AND KAWAUCHI, G K The local implantation of sulfamidamide in the peritoneal cavity and its clinical application in peritonitis, 671

- THEIS, FRANK V., AND FREELAND, M. R.  
Thromboangiitis obliterans, 101  
TURNER, OSCAR A., CRAIG, WINCHELL  
McK., AND KERNOHAN, JAMES  
W. Malignant meningiomas, 81

## V

- VISSCHER, MAURICE B., BALL, ZELDA B.,  
BARNES, RICHARD H., AND  
SIVERTSEN, IVAR. The influence  
of caloric restriction upon the  
incidence of spontaneous mam-  
mary carcinoma in mice, 48

## W

- WADE, LEO J. (See Quinn, Lord, and  
Wade), 229  
— (See Quinn, Lord, and Wade), 233  
WALDRON, CARL W., AND BALKIN, SAM-  
UEL G. Fractures of the max-  
illa, 183  
WANGENSTEEN, OWEN H. (See Kremen,  
Hall, Koschnitzke, Stevens, and  
Wangensteen), 333

- WAUGH, JOHN M., HERRELL, WALLACE  
E., AND CRUMPACKER, LEO K.  
Peptic ulcer in Meckel's di-  
verticulum causing intrinsic in-  
testinal obstruction, 385

- WEED, JOHN C., AND COLLINS, CONRAD G.  
Cystic degeneration of the  
ovaries, 292

- WEISMAN, SYDNEY. (See Sperling, Weis-  
man, and Papermaster), 600

- WHITE, EDGAR H. Polyostotic fibrous  
dysplasia, 607

- WILLIAMS, WILLIAM H. (See Sparkman  
and Williams), 698

- WILTRAKIS, G. A. (See Partipilo and  
Wiltrakis), 557

- WOODWARD, FLETCHER D. (See Drash  
and Woodward), 886

- WRENN, FRANK, AND FEDER, J. M. As-  
piration biopsy, 456

## Y

- YOUNG, FORREST. Function of the lower  
jaw following partial resection,  
966

## SUBJECT INDEX\*

Book reviews are indicated by (B. Rev.) after the page number, editorials by (E) after the page number.

### A

- A, vitamin, content of plasma and hepatic tissue biopsied at operation: effects of preoperative therapy in obstructive jaundice (Stewart and Rourke), 939
- Abdominal wall, gas gangrene of (Quinn et al.), 233
- Accidental injuries, 988 (B. Rev.)
- Adenoma of lung, malignant (Adams et al.), 503
- Adhesions, dense, method of mobilizing spleen in presence of (Rives), 223
- peritoneal, prophylaxis of (Boys), 118
- Aged individuals, carcinoma of stomach in, surgical treatment of (Bowen), 869
- Air blast, cold, use of, on precancerous skin lesions and hemangiomas (Poppe), 460
- Alimentary azotemia, experimental studies on (Chunn et al.), 56
- American Academy of Orthopedic Surgeons, tenth annual convention, review of meeting of, Atlantic City, N. J., Jan. 11-15, 1942 (Cox), 832
- Aminophylline, ethylene diamine, effect of intravenous theophylline with, upon rate and depth of respiration (Speiling et al.), 600
- Anesthesia, blood studies during (Martin and Robertson), 11
- intravenous pentothal sodium (Long and Ochsner), 474
- Angina, Ludwig's (Taffel and Harvey), 841
- Anticus, scalenus, factor in congenital torticollis (Copland), 624
- Anus and rectum, congenital malformations of (Harken), 422
- sigmoid colon. diagnosis and treatment, 501 (B. Rev.)
- Appendicitis peritonitis, pathogenicity of bacteria of (Altemeier), 374
- Appliance, simplified, for craniomaxillary support and fixation in fractures of maxilla (Waldron and Brillan), 183

- Arterial blood oxygen studies during treatment of thromboangitis obliterans, with sodium tetrathionate and sodium thiosulfate, clinical observations and (Theis and Freeland), 101
- Aspiration biopsy (Wrenn and Feder), 456
- Atelectasis in dogs, experimental (Keeley and Gibson), 527
- Azotemia, alimentary, experimental studies on (Chunn et al.), 56

### B

- Bacteria of appendicitis peritonitis, pathogenicity of (Altemeier), 374
- Bile duct, common, sphincter mechanism of, in human subjects (Bergh), 299
- salts, effect of, on recovery of liver function after release of common duct obstruction (Berman et al.), 1
- Bismuth in kidney, localization of (Kroll et al.), 810
- Blood absorption, site of, and experimental studies on alimentary azotemia (Chunn et al.), 56
- bank and technique and therapeutics of transfusion, 989 (B. Rev.)
- flow, pulmonary, effect of experimental atelectasis in dogs on (Keeley and Gibson), 527
- gases, effect of experimental atelectasis in dogs on (Keeley and Gibson), 527
- oxygen, arterial, studies during treatment of thromboangitis obliterans with sodium tetrathionate and sodium thiosulfate, clinical observations and (Theis and Freeland), 101
- studies during anesthesia (Martin and Robertson), 11
- Bone, transplanted, effect of sulfamidamide crystals, used topically, on fate of (Horwitz), 690
- tumors with reference to their treatment (Copeland), 176

\*January, pp. 1-168. February, pp. 169-332. March, pp. 333-502. April, pp. 503-670. May, pp. 671-840. June, pp. 841-1004

Book reviews, 331-332, 501-502, 669, 988-990

Books received, 669-670

Bovine plasma, whole, and serum to man, intravenous administration of (Kremen et al.), 333

Breast, carcinoma of (Stabins and Dowdy), 898

Burns, shock in, nervous factor in etiology of (Kabat and Hedin), 766 and their relation to ulcer, experimental investigation of gastrointestinal secretions and motility following (Necheles and Olson), 751

treatment of (Oxford War Manuals), 501 (B. Rev.)

C

Callus, influence of hypoproteinemia on formation of, in experimental fracture (Rhoads and Kasin-skas), 38

Caloric restriction, influence of, upon incidence of spontaneous mammary carcinoma in mice (Vis-scher et al.), 48

Carbuncles, large, surgical treatment of, in diabetic and nondiabetic individuals (McLaughlin), 797

Carcinoma, breast (Stabins and Dowdy), 898

cervix, intestinal obstruction as phase of (Pearson and Garcia), 636

colon and rectum, recent advances in surgical treatment of (Cattell and Sugarbaker), 644

spontaneous mammary, in mice, influence of caloric restriction upon incidence of (Visscher et al.), 48

stomach in aged individuals, surgical treatment of (Bowers), 869

Carcinoma-like tumors of lung with long clinical course (Adams et al.), 503

Carotid sinus reflex in man, observations and surgical aspects of (Ray and Stewart), 915

Cephalin-cholesterol flocculation test in jaundiced patient (Nadler and Butler), 732

Cerebral fungus: treatment by skin grafting; on major wounds of skull (Hyndman), 466

Cervix, carcinoma of, intestinal obstruction as phase of (Pearson and Garcia), 636

Children and infants, distribution and transport of gas in gastro-intestinal tract of (Paine and Nessa), 281

Cholorrhea, postoperative (Keating et al.), 198

Chyle, aspirated, effects of reintroduction of; chylothorax and chylo-peritoneum (Little et al.), 392

Chyloperitoneum and chylothorax (Little et al.), 392

Chylothorax and chyloperitoneum (Little et al.), 392

Circulation time, effect of experimental atelectasis in dogs on (Keeley and Gibson), 527

Circulatory collapse, profound peripheral, due to excessive loss of fluid and electrolytes through a T-tube; postoperative cholorrhea (Keating et al.), 198

Civil and military practice, traumatic injuries to peripheral vessels in (Gage), 983 (E)

Clinics, surgical, of North America, 990 (B. Rev.)

Coagulability, blood, photo-electric study of, in hemorrhagic diseases, 502 (B. Rev.)

Cold air blast, use of, on precancerous skin lesions and hemangiomas (Poppe), 460

and heat, comparison of effects of local application of, in prevention and treatment of experimental traumatic shock (Blacklock), 356

Colon and rectum, carcinoma of, recent advances in surgical treatment of (Cattell and Sugarbaker), 644

Colonic resection, partial, gastrointestinal motility in dog following, and ileocolostomy (Kozoll and Necheles), 360

Common duct obstruction, effect of bile salts on recovery of liver function after release of (Berman et al.), 1

Congenital double septum with cyst formation, obstruction of stomach due to (Metz et al.), 586

malformations of rectum and anus (Harken), 422

torticollis, scalenus anticus factor in (Copland), 624

Cotton suture material, employment of, in field (Sparkman and Williams), 698

Crystals, sulfanilamide, effect of, used topically, on fate of transplanted bone (Horwitz), 690

Cyst formation, congenital double septum with, obstruction of stomach due to (Metz et al.), 586

Cystic degeneration of ovaries (Weed and Collins), 292

Cysts, hemorrhagic, of lungs; cases in which marsupialization was done (Gray and Skinner), 777

spinal extradural (Mayfield and Grantham), 589



## SUBJECT INDEX\*

Book reviews are indicated by (B. Rev.) after the page number; editorials by (E) after the page number.

### A

- A, vitamin, content of plasma and hepatic tissue biopsied at operation: effects of preoperative therapy in obstructive jaundice (Stewart and Rourke), 939
- Abdominal wall, gas gangrene of (Quinn et al.), 233
- Accidental injuries, 988 (B. Rev.)
- Adenoma of lung, malignant (Adams et al.), 503
- Adhesions, dense, method of mobilizing spleen in presence of (Rives), 223
- peritoneal, prophylaxis of (Boys), 118
- Aged individuals, carcinoma of stomach in, surgical treatment of (Bowers), 869
- Air blast, cold, use of, on precancerous skin lesions and hemangiomas (Poppe), 460
- Alimentary azotemia, experimental studies on (Chunn et al.), 56
- American Academy of Orthopedic Surgeons, tenth annual convention, review of meeting of, Atlantic City, N. J., Jan. 11-15, 1942 (Cox), 832
- Aminophylline, ethylene diamine, effect of intravenous theophylline with, upon rate and depth of respiration (Sperling et al.), 600
- Anesthesia, blood studies during (Martin and Robertson), 11
- intravenous pentothal sodium (Long and Ochsner), 474
- Angina, Ludwig's (Taffel and Harvey), 841
- Anticus, scalenus, factor in congenital torticollis (Copland), 624
- Anus and rectum, congenital malformations of (Harken), 422
- sigmoid colon: diagnosis and treatment, 501 (B. Rev.)
- Appendicitis peritonitis, pathogenicity of bacteria of (Altemeier), 374
- Appliance, simplified, for craniomaxillary support and fixation in fractures of maxilla (Waldron and Balkin), 183

- Arterial blood oxygen studies during treatment of thromboangiitis obliterans, with sodium tetrathionate and sodium thiosulfate, clinical observations and (Theis and Freeland), 101
- Aspiration biopsy (Wrenn and Feder), 456
- Atelectasis in dogs, experimental (Keeley and Gibson), 527
- Azotemia, alimentary, experimental studies on (Chunn et al.), 56

### B

- Bacteria of appendicitis peritonitis, pathogenicity of (Altemeier), 374
- Bile duct, common, sphincter mechanism of, in human subjects (Bergh), 299
- salts, effect of, on recovery of liver function after release of common duct obstruction (Berman et al.), 1
- Bismuth in kidney, localization of (Kroll et al.), 810
- Blood absorption, site of, and experimental studies on alimentary azotemia (Chunn et al.), 56
- bank and technique and therapeutics of transfusion, 989 (B. Rev.)
- flow, pulmonary, effect of experimental atelectasis in dogs on (Keeley and Gibson), 527
- gases, effect of experimental atelectasis in dogs on (Keeley and Gibson), 527
- oxygen, arterial, studies during treatment of thromboangiitis obliterans with sodium tetrathionate and sodium thiosulfate, clinical observations and (Theis and Freeland), 101
- studies during anesthesia (Martin and Robertson), 11
- Bone, transplanted, effect of sulfanilamide crystals, used topically, on fate of (Horwitz), 690
- tumors with reference to their treatment (Copeland), 436

\*January, pp. 1-168; February, pp. 169-332; March, pp. 333-502; April, pp. 503-670; May, pp. 671-840; June, pp. 841-1004.

## G

- Gall bladder, gas in, clinical significance of (McCorkle and Fong), 851
- Gangrene, gas, of abdominal wall (Quinn et al.), 233
- Gas, distribution and transport of, in gastrointestinal tract of infants and young children, observations on (Paine and Nessa), 281
- in gall bladder, clinical significance of (McCorkle and Fong), 851
- gangrene of abdominal wall (Quinn et al.), 233
- Gastrointestinal motility in dog following ileocolostomy and partial colonic resection (Kozoll and Necheles), 360
- secretions, and motility following burns and their relation to ulcer, experimental investigation of (Necheles and Olson), 751
- tract, of infants and young children, distribution and transport of gas in (Paine and Nessa), 281
- Glucose infusion, intravenous, shock and hyperpyrexia induced by (Medoff and Burton), 596
- Goiter, toxic, acute iodism during treatment of (Guptill), 962

## H

- Heat and cold, comparison of effects of local application of, in prevention and treatment of experimental traumatic shock (Blacklock), 356
- Hemangioma of liver (Shumacker), 209
- Hemangiomas and precancerous skin lesions, use of cold air blast on (Poppe), 460
- Hematocrit, effect of experimental atelectasis in dogs on (Keeley and Gibson), 527
- Hemoglobin, effect of experimental atelectasis in dogs on (Keeley and Gibson), 527
- Hemorrhagic cysts of lung, cases in which marsupialization was done (Gray and Skinner), 777
- diseases, photoelectric study of blood coagulability, 502 (B. Rev.)
- Hepatic function, Quick hippuric acid test in (Campbell), 195
- tissue and plasma, vitamin A content of, biopsied at operation, effects of preoperative therapy in obstructive jaundice (Stewart and Rourke), 939
- Hip, impacted fracture of (Hart), 472 (E)
- Hippuric acid test, Quick, in hepatic function (Campbell), 195

- Human being and dog, mechanism of action of prostigmine on intestinal motility in (Schwartz et al.), 746
- Hyperpyrexia and shock induced by intravenous glucose infusion (Medoff and Burton), 596
- Hypertension, acute renal (Quinby and Simeone), 544
- Hyperthyroidism, preoperative and postoperative treatment of, use of estrogenic substances in (Storek and Holcombe), 703
- Hypertrophy, unilateral, of masseter muscle (Coffey), 815
- Hypoproteinemia, influence of, on formation of callus in experimental fracture (Rhoads and Kasinskas), 38

## I

- Ileocolostomy and partial colonic resection, gastrointestinal motility in dog following (Kozoll and Necheles), 360
- Impacted fracture of hip (Hart), 472 (E)
- Infants and young children, distribution and transport of gas in gastrointestinal tract of (Paine and Nessa), 281
- Infections, Welch bacillus, arising from stomach and duodenum (Quinn et al.), 229
- Injections, procaine, of sympathetic nerves, value of skin resistance studies in determining accuracy of (Shumacker), 949
- Injuries, accidental, 988 (B. Rev.)
- traumatic, to peripheral vessels in both civil and military practice (Gage), 983 (E)
- Instrument, improved, observations with, on aspiration biopsy (Wrenn and Feder), 456
- Interstitial nephritis, exudative, pyelo-nephritis (Bell), 261
- Intervertebral disc, with special reference to rupture of annulus fibrosus with herniation of nucleus pulposus, 331 (B. Rev.)
- Intestinal lipodystrophy, or Whipple's disease (Pearse), 906
- motility, mechanism of action of prostigmine on, in human being and dog (Schwartz et al.), 746
- obstruction, as phase of carcinoma of cervix (Pearson and Garcia), 636
- evaluation of intestinal suction in (Blodgett), 739
- intrinsic, peptic ulcer in Meckel's diverticulum causing (Vaughan et al.), 385
- suction in intestinal obstruction, an evaluation of (Blodgett), 739

## D

- Degeneration, cystic, of ovaries (Weed and Collins), 292
- Diabetic and nondiabetic individuals, surgical treatment of large carbuncles in (McLaughlin), 797
- Diamine, ethylene (aminophylline), effect of intravenous theophylline with, upon rate and depth of respiration (Sperling et al.), 600
- Disease, thyroid, skeletal manifestations of (Bodenheimer and Barchani), 710
- Whipple's, or intestinal lipodystrophy (Pearse), 906
- Distribution and transport of gas in  
et of infants  
(Paine and  
Nessa), 281
- Diverticulum, Meckel's, peptic ulcer in, causing intrinsic intestinal obstruction (Vaugh et al.), 385
- Dog and human being, mechanism of action of prostigmine on intestinal motility in (Schwartz et al.), 746
- Duct, common bile, sphincter mechanism of, in human subjects (Bergh), 299
- obstruction, common, effect of bile salts on recovery of liver function after release of (Berman et al.), 1
- Duodenal obstruction (Partipilo and Wiltrakis), 557
- Duodenum, and stomach, Welch bacillus infections arising from (Quinn et al.), 229
- Dynamic changes in experimental pulmonary embolism (Megibow et al.), 19
- Dysplasia, polyostotic fibrous (White), 607

## E

- Editorials, 472, 819, 983
- Electrolytes, excessive loss of fluid and, through a T-tube, profound peripheral circulatory collapse due to, postoperative cholorrhea (Keating et al.), 198
- Embolism, experimental pulmonary, dynamic changes in (Megibow et al.), 19
- Endoscopy, intraspinal (Pool), 169
- Esophageal strictures, impenetrable, treatment of, by combined intrasophageal and extraesophageal approach (Drash and Woodward), 886
- Esophagogastrostomy, transthoracic (Holman and McSwain), 882

- Estrogenic substances, use of, in preoperative and postoperative treatment of hyperthyroidism (Storek and Holcombe), 703
- Ethylene diamine (aminophylline), effect of intravenous theophylline with, upon rate and depth of respiration (Sperling et al.), 600
- Etiology of shock in burns, nervous factor in (Kabat and Hedin), 766
- Experimental fracture, influence of hypoproteinemia on the formation of callus in (Rhoads and Kasinskas), 38
- pulmonary embolism, dynamic changes in (Megibow et al.), 19
- studies on alimentary azotemia (Chunn et al.), 56
- Extradural cysts, spinal (Mayfield and Grantham), 589
- Extraesophageal and intraesophageal approach, combined, treatment of impenetrable esophageal strictures by (Drash and Woodward), 886
- Extremities, positioning in surgery of (Cozen), 605
- Extremity, relatively ischemic, use of refrigeration combined with vasodilatation to preserve vitality in (Ochsner), 819 (E)
- Exudative interstitial nephritis, pyelonephritis (Bell), 261

## F

- Facial tic, spasmodic, surgical treatment of (German), 912
- Fever, rat-bite (Rogliano), 632
- Flocculation test, cephalin-cholesterol, in jaundiced patient (Nadler and Butler), 732
- Fluid and electrolytes, excessive loss of, through a T-tube, profound peripheral circulatory collapse due to; postoperative cholorrhea (Keating et al.), 198
- Fracture, experimental, influence of hypoproteinemia on the formation of callus in (Rhoads and Kasinskas), 38
- of hip, impacted (Hart), 472 (E)
- supracondylar, reduction of, in children (Hart), 23
- Fractures of maxilla (Waldron and Balkin), 183
- Fungus, cerebral; treatment by skin grafting, on major wounds of skull (Hyndman), 466
- Fusospirochetal onychia and paronychia (Benedek), 75

## O

- Obliterans, thromboangiitis (Theis and Freeland), 101
- Obstruction, duodenal (Partipilo and Wiltrakis), 557
- intestinal, and evaluation of intestinal suction in (Blodgett), 739
- as phase of carcinoma of cervix (Pearson and Garcia), 636
- intrinsic intestinal, peptic ulcer in Meckel's diverticulum causing (Waugh et al.), 385
- of stomach due to congenital double septum with cyst formation (Metz et al.), 586
- Onychia and paronychia, fusospirochetal (Benedek), 75
- Ovaries, cystic degeneration of (Weed and Collins), 292
- Oxygen, arterial blood, studies during treatment of thromboangiitis obliterans with sodium tetrathionate and sodium thiosulfate, clinical observations and (Theis and Freeland), 101

## P

- Pancreas, recent surgical physiology of (Siegel), 821
- Paravertebral thoracoplasty for treatment of pulmonary tuberculosis (Adie et al.), 788
- Paronychia and onychia, fusospirochetal (Benedek), 75
- Parotitis, secondary or postoperative (Madding and Fricke), 45
- Pathogenicity of bacteria of appendicitis peritonitis (Altemeier), 374
- Pentothal sodium anesthesia, intravenous (Long and Ochsner), 474
- Peptic ulcer in Meckel's diverticulum causing intrinsic intestinal obstruction (Waugh et al.), 385
- Peripheral circulatory collapse, profound, due to excessive loss of fluid and electrolytes through a T-tube; postoperative cholorrhea (Keating et al.), 198
- vessels, traumatic injuries to, in both civil and military practice (Gage), 983 (E)
- Peritoneal adhesions, prophylaxis of (Boys), 118
- cavity, local implantation of sulfanilamide in, and its clinical application in peritonitis (Tashiro et al.), 671
- protection, action of sulfonamide drugs in experimental peritonitis (Harvey et al.), 244

- Peritonitis (Harvey et al.), 244
- appendicitis, pathogenicity of bacteria of (Altemeier), 374
- clinical application in, local implantation of sulfanilamide in peritoneal cavity and (Tashiro et al.), 671
- Photo-electric study of blood coagulability; hemorrhagic diseases, 502 (B. Rev.)
- Physiology, Macleod's, in modern medicine, 331 (B. Rev.)
- recent surgical, of pancreas (Siegel), 821
- Pilonidal sinuses occurring over higher spinal segments, involving spinal cord (Kooistra), 63
- Plasma, vitamin A content of, and hepatic tissue biopsied at operation; effects of preoperative therapy in obstructive jaundice (Stewart and Rourke), 939
- volume, effect of experimental atelectasis in dogs on (Keeley and Gibson), 527
- whole bovine, and serum to man, intravenous administration of (Kremen et al.), 333
- Polyostotic fibrous dysplasia (White), 607
- Positioning in surgery of extremities (Cozen), 605
- Postoperative cholorrhea (Keating et al.), 198
- and preoperative treatment of hyperthyroidism, use of estrogenic substances in (Storek and Holcombe), 703
- or secondary parotitis (Madding and Fricke), 45
- Precancerous skin lesions and hemangiomas, use of cold air blast on (Poppe), 460
- Preoperative and postoperative treatment of hyperthyroidism, use of estrogenic substances in (Storek and Holcombe), 703
- therapy, effects of, in obstructive jaundice, vitamin A content of plasma and hepatic tissue biopsied at operation (Stewart and Rourke), 939
- Prevention and treatment of experimental traumatic shock, comparison of effects of local application of heat and cold in (Blalock), 356
- Procaine injections of sympathetic nerves, value of skin resistance studies in determining accuracy of (Shumacker), 949
- Prophylaxis of peritoneal adhesions (Boys), 118

- Intraesophageal and extraesophageal approach combined, treatment of impenetrable esophageal strictures by (Drash and Woodward), 886
- Intraspinal endoscopy (Pool), 169
- Intravenous administration of whole bovine plasma and serum to man (Kremen et al.), 333
- glucose infusion, shock and hyperpyrexia induced by (Medoff and Burton), 596
- pentothal sodium anesthesia (Long and Ochsner), 474
- theophylline with ethylene diamine (aminophylline) upon rate and depth of respiration (Sperling et al.), 600
- Iodism, acute, during treatment of toxic goiter (Guptill), 962
- Ischemic extremity, relatively, use of refrigeration combined with vasodilatation to preserve vitality in (Ochsner), 819 (E)
- J
- Jaundice, obstructive, effects of preoperative therapy in, vitamin A content of plasma and hepatic tissue biopsied at operation (Stewart and Rourke), 939
- Jaundiced patient, cephalin-cholesterol flocculation test in (Nadler and Butler), 732
- Jaw, lower, function of, following partial resection (Young), 966
- K
- Kidney, localization of bismuth in (Kroll et al.), 810
- L
- Lipodystrophy, intestinal, or Whipple's disease (Pearse), 906
- Liver function, effect of bile salts on recovery of, after release of common duct obstruction (Berman et al.), 1
- hemangioma of (Shumacker), 209
- Localization of bismuth in kidney (Kroll et al.), 810
- Ludwig's angina (Taffel and Harvey), 841
- Lung, hemorrhagic cysts of; cases in which marsupialization was done (Gray and Skinner), 777
- malignant adenoma of (Adams et al.), 503
- M
- Macleod's physiology in modern medicine, 331 (B. Rev.)
- Malformations, congenital, of rectum and anus (Harken), 422
- Malignant adenoma of lung (Adams et al.), 503
- meningiomas (Turner et al.), 81
- Mammary, carcinoma, spontaneous, in mice, influence of caloric restriction upon incidence of (Vischer et al.), 48
- Marsupialization, report of two cases done for hemorrhagic cysts of lung (Gray and Skinner), 777
- Masseter muscle, unilateral hypertrophy of (Coffey), 815
- Maxilla, fractures of (Waldron and Balkin), 183
- Mechanism of action of prostigmine on intestinal motility in human being and in dog (Schwartz et al.), 746
- Meckel's diverticulum, peptic ulcer in, causing intrinsic intestinal obstruction (Waugh et al.), 385
- Medical science, introduction to, 989 (B. Rev.)
- Meetings, review of recent, 496, 653, 832, 987
- Meningiomas, malignant (Turner et al.), 81
- Mice, spontaneous mammary carcinoma in, influence of caloric restriction upon incidence of, (Vischer et al.), 48
- Military and civil practice, traumatic injuries to peripheral vessels in (Gage), 983 (E)
- Mobilizing spleen, method of, in presence of dense adhesions (Rives), 223
- Motility and gastrointestinal secretions following burns and their relation to ulcer, experimental investigation of (Neeches and Olson), 751
- intestinal, mechanism of action of prostigmine on, in human being and dog (Schwartz et al.), 746
- Muscle, masseter, unilateral hypertrophy of (Coffey), 815
- Myeloscapy; intraspinal endoscopy (Pool), 169
- N
- Nephritis, exudative interstitial, pyelonephritis (Bell), 261
- Nerves, sympathetic, procaine injections of, value of skin resistance studies in determining accuracy of (Shumacker), 919
- Nervous factor in etiology of shock in burns (Kabat and Hedlin), 766
- Neuroanatomy, 988 (B. Rev.)
- Nondiabetic and diabetic individuals, surgical treatment of large carbuncles in (McLaughlin), 797

- Spinal cord membranes and its roots, surgical diseases of, 669 (B. Rev.)
- pilonidal sinuses occurring over higher spinal segments involving (Kooistra), 63
- extradural cysts (Mayfield and Grant ham), 589
- segments, higher, pilonidal sinuses occurring over, involving spinal cord (Kooistra), 63
- Spleen, method of mobilizing, in presence of dense adhesions (Rives), 223
- Splenectomy (Rives), 223
- Stomach, carcinoma of, in aged individuals, surgical treatment of (Bowers), 869
- and duodenum, Welch bacillus infections arising from (Quinn et al.), 229
- obstruction of, due to congenital double septum with cyst formation (Metz et al.), 586
- Strictures, impenetrable esophageal, treatment of, by combined intraesophageal and extraesophageal approach (Drash and Woodward), 886
- Suction, intestinal, an evaluation of, in intestinal obstruction (Blolett), 739
- Sulfanilamide crystals, effect of, used topically, on fate of transplanted bone (Horwitz), 690
- local implantation of, in peritoneal cavity and its clinical application in peritonitis (Tashiro et al.), 671
- Sulfonamide drugs, action of, in experimental peritonitis, studies in peritoneal protection with particular reference to (Harvey et al.), 244
- Supracondylar fracture, reduction of, in children (Hart), 33
- Surgeons, Society of University, 987
- Surgery of extremities, positioning in (Cozen), 605
- Surgical aspects of carotid sinus reflex in man (Ray and Stewart), 915
- clinics of North America, 990 (B. Rev.)
- diseases of spinal cord membranes and its roots, 669 (B. Rev.)
- management of varicose veins: importance of individualization in choice of procedure (Harkins and Sehug), 402
- physiology, recent, of pancreas (Siegel), 821
- treatment of carcinoma of colon and rectum, recent advances in (Cattell and Sugarbaker), 614
- of stomach in aged individuals (Bowers), 869
- Surgical treatment—Cont'd
- of large carbuncles in diabetic and nondiabetic individuals (McLaughlin), 797
- of spasmodic facial tic (German), 912
- Suture material, cotton, employment of, in field (Sparkman and Williams), 698
- Sympathetic nerves, procaine injections of, value of skin resistance studies in determining accuracy of (Shumaker), 949
- T
- Tetrathionate, sodium, and sodium thiosulfate, clinical observations and arterial blood oxygen studies during treatment of thromboangiitis obliterans with (Theis and Freeland), 101
- Theophylline, intravenous, effect of, with ethylene diamine (aminophylline) upon rate and depth of respiration (Sperling et al.), 600
- Therapy, preoperative, effects of, in obstructive jaundice, vitamin A content of plasma and hepatic tissue biopsied at operation (Stewart and Rourke), 939
- Thiosulfate, sodium and sodium tetrathionate, clinical observations and arterial blood oxygen studies during treatment of thromboangiitis obliterans with (Theis and Freeland), 101
- Thoracoplasty, paravertebral, for treatment of pulmonary tuberculosis (Adie et al.), 788
- Thromboangiitis obliterans (Theis and Freeland), 101
- Thyroid disease, skeletal manifestations of (Bodenheimer and Barham), 710
- Tic, facial, spasmodic, surgical treatment of (German), 912
- Torticollis, congenital, scalenus anticus factor in (Copland), 624
- Toxic goiter, acute iodism during treatment of (Guptill), 962
- Transfusion, therapeutics and technique of, and blood bank, 989 (B. Rev.)
- Transplanted bone, fate of, effect of sulfanilamide crystals, used topically (Horwitz), 690
- Transport and distribution of gas in gastrointestinal tract of infants and young children (Paine and Nesha), 281
- Transthoracic esophagogastronomy (Holman and McSwain), 882

- Prostigmine, mechanism of action, on intestinal motility in human being and dog (Schwartz et al.), 746
- Pulmonary blood flow, effect of experimental atelectasis in dogs on (Keeley and Gibson), 527
- embolism, experimental, dynamic changes in (Megibow et al.), 19
- tuberculosis, paravertebral thoracoplasty for treatment of (Adie et al.), 788
- Pyelonephritis, exudative interstitial nephritis (Bell), 261
- Q
- Quick hippuric acid test, in hepatic function (Campbell), 195
- R
- Rat-bite fever, two cases of (Rogliano), 632
- Rectum and anus, congenital malformations of (Harken), 422
- anus, sigmoid colon: diagnosis and treatment, 501 (B. Rev.)
- and colon, carcinoma of, recent advances in surgical treatment of (Cattell and Sugarbaker), 644
- Reduction of supracondylar fracture in children (Hart), 33
- Reflex, carotid sinus, in man, observations and surgical aspects of (Ray and Stewart), 915
- Refrigeration, use of, combined with vasodilatation to preserve vitality in a relatively ischemic extremity (Ochsner), 819 (E)
- Renal hypertension, acute (Quinby and Simeone), 544
- Resection, partial colonic, gastrointestinal motility in dog following ileocolostomy and (Kozoll and Neecheles), 360
- function of lower jaw following (Young), 966
- Respiration, rate and depth, effect of intravenous theophylline with ethylene diamine (aminophylline) upon (Sperling et al.), 600
- Restriction, caloric, influence of, upon incidence of spontaneous mammary carcinoma in mice (Vischer et al.), 48
- S
- Sealens anticus factor in congenital torticollis (Copland), 624
- Science, medical, introduction to, 989 (B. Rev.)
- Secondary or postoperative parotitis (Madding and Fricke), 45
- Secretions, gastrointestinal, and motility following burns and their relation to ulcer (Neecheles and Olson), 751
- Segments, higher spinal, pilonidal sinuses occurring over, involving spinal cord (Kooistra), 63
- Septum, double, congenital, with cyst formation, obstruction of stomach due to (Metz et al.), 586
- Serum, and whole bovine plasma to man, intravenous administration of (Kremen et al.), 333
- Shock, in burns, nervous factor in etiology of (Kabat and Hedin), 766
- experimental traumatic, comparison of effects of local application of heat and cold in prevention and treatment of (Blalock), 356
- and hyperpyrexia induced by intravenous glucose infusion (Medoff and Burton), 596
- Sigmoid colon, anus, rectum: diagnosis and treatment, 501 (B. Rev.)
- Sinuses, pilonidal, occurring over higher spinal segments involving spinal cord (Kooistra), 63
- Skeletal manifestations of thyroid disease (Bodenheimer and Bar-cham), 710
- Skin grafting, treatment by, for cerebral fungus (Hyndman), 466
- resistance studies, value of, in determining accuracy of procaine injections of sympathetic nerves (Shumacker), 949
- Skull, major, wounds of, treatment of (Hyndman), 466
- Society of University Surgeons, 987
- Sodium anesthesia, pentothal, intravenous (Long and Ochsner), 474
- tetrathionate and sodium thiosulfate, clinical observations and arterial blood oxygen studies during treatment of thromboangiitis obliterans with (Theis and Freeland), 101
- thiosulfate, and sodium tetrathionate, clinical observations and arterial blood oxygen studies during treatment of thromboangiitis obliterans with (Theis and Freeland), 101
- Southern Medical Association, meeting of, Urological Section of, St. Louis, Mo., Nov. 12 & 13, 1941 (Spence), 496
- Surgical Association meeting, Dec. 9-11, 1941, Pinehurst, N. C., review of (Poer and Horsley), 653
- Spasmodic facial tic, surgical treatment of (German), 912
- Sphincter mechanism of common bile duct in human subjects (Bergh), 299





- Traumatic injuries to peripheral vessels in both civil and military practice (Gage), 983 (*E*)
- shock, experimental, comparison of effects of local application of heat and cold in prevention and treatment of (Blalock), 356
- Treatment of patient past fifty, 988 (B. Rev.)
- surgical, of carcinoma of colon and rectum, recent advances in (Cattell and Sugarbaker), 644
- of stomach in aged individuals (Bowers), 869
- of spasmodic facial tic (German), 912
- Tuberculosis, pulmonary, paravertebral thoracoplasty for treatment of (Adie et al.), 788
- Tumors, bone, with reference to their treatment (Copeland), 436
- of lung, carcinoma-like, with long clinical course (Adams et al.), 503

## U

- Ulcer, experimental investigation of gastrointestinal secretions and motility following burns and their relation to (Necheles and Olson), 751
- peptic, in Meckel's diverticulum causing intrinsic intestinal obstruction (Vaughn et al.), 385
- Unilateral hypertrophy of masseter muscle (Coffey), 815

- Urological section of Southern Medical Association, meeting of, St. Louis, Mo., Nov. 12. & 13, 1941 (Spence), 496

## V

- Varicose veins, surgical management of, importance of individualization in choice of procedure (Harkins and Schug), 402
- Vasodilatation, use of refrigeration combined with, to preserve vitality in a relatively ischemic extremity (Ochsner), 819 (*E*)
- Veins, varicose, surgical management of, importance of individualization in choice of procedure (Harkins and Schug), 402
- Vessels, peripheral, traumatic injuries to, in both civil and military practice (Gage), 983 (*E*)
- Vitamin A content of plasma and hepatic tissue biopsied at operation; effects of preoperative therapy in obstructive jaundice (Stewart and Rourke), 939

## W

- Welch bacillus infections arising from stomach and duodenum (Quinn et al.), 229
- Whipple's disease, or intestinal lipodystrophy (Pearse), 906
- Wounds of skull, major, treatment of (Hyndman), 466

